The New England
Journal of Medicine

Copyright, 1950, by the Massachusetts Medical Society

Volume 243 AUGUST 3, 1950 Number 5

MULTIPLE-BALLOON KYMOGRAPHIC RECORDING OF THE COMPARATIVE ACTION OF DEMEROL, MORPHINE AND PLACEBOS ON THE MOTILITY OF THE UPPER SMALL INTESTINE IN MAN*

WILLIAM P. CHAPMAN, M.D.,† EIRWYN N. ROWLANDS, M.D.,‡ AND CHESTER M. JONES, M.D.§

BOSTON

NUMEROUS claims have been made that Demerol, in addition to its analgesic properties, has a spasmolytic or relaxing action on the motility of the intestinal tract. Eisleb and Schaumann,[1] who in 1939 synthesized Demerol, and Duguid and Heathcote[2] were among the first to report that this drug exerted an antispasmodic effect on smooth muscle of the intestine in animals. In 1942 Batterman,[3] using the balloon intubation method, observed an antispasmodic action of the drug on the gastrointestinal tract in man. In a later publication he claimed that with 50 to 100 mg. of Demerol administered intramuscularly an antispasmodic action was obtained from various portions of the intestine in 84 per cent of 27 human subjects; complete cessation or diminution of motility was found to occur usually within ten minutes, and the effect lasted from fifteen to over ninety minutes.[4] In another report Batterman and Himmelsbach[5] appeared to have made a somewhat different interpretation of the earlier results with the statement that "segmental contractions and tone are diminished or abolished while propulsive action is unaltered." Yonkman, Noth and Hecht[6] noted differences in the intestinal action of Demerol in dogs as compared to man. In the dog intestinal motility was uniformly stimulated; in 3 cases in human beings they believed that partial relaxation of the gut occurred. The stimulating effect on the small intestine of the dog was also reported by Gruber et al.[7] In the unanesthetized dogs Demerol, when given intravenously, was associated with an increase in "tone" and usually with an increase in peristaltic activity and in the force of rhythmic contractions, which were seen to last for longer than an hour. These authors inferred that in relieving intestinal colic, the effect of the drug must be attributed to its analgesic potency rather than to a smooth-muscle-relaxing action.

The bulk of evidence appears to be, therefore, that in man Demerol has a depressing effect on intestinal motility. In contrast, it is claimed that morphine increases the "tone" of the human intestine.[8]

Our studies have been concerned with the action of Demerol on the upper small intestine in man. Its effect has been compared to the action of morphine as well as to the changes in motility following the administration of placebos. The comparative results with the two latter agents will be reported elsewhere.[9, 10] Eight subjects were studied with Demerol, 4 being healthy adults and 4, patients without lesions of the alimentary tract. Five of these subjects were tested both with placebos and with morphine. For comparison Demerol was given subcutaneously in a dosage of 100 mg. Morphine was administered in the same manner in a dosage of 10 mg. Motor activity was recorded graphically with a multiple-balloon water manometer system. The effect of the agents was noted particularly on propulsive and nonpropulsive contractions and on "tone."

METHOD

The test procedure, including the method of recording and assessing the tracings and the technic of drug and placebo administration, has been described in previous communications.[9, 11, 12] One study was carried out with four balloons, three with two balloons, three with three balloons, and one with one balloon in the upper small intestine (duodenum or upper jejunum or both areas). The balloons were about 5 cm. in length and were spaced at intervals of 10 cm. Before the administration of Demerol, motor activity was recorded for an average of fifty-eight minutes, with a range of forty-five to seventy minutes. After the drug had been given the motility was recorded for an average period of two hundred and forty minutes, with a range

*From the Medical Services, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School.
Supported by grants from G. D. Searle and Company, Chicago, Illinois, and Hoffmann-LaRoche, Incorporated, Nutley, New Jersey.
†Instructor in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.
‡Instructor, University College Hospital Medical School, London, England; formerly, research fellow in medicine, Harvard Medical School.
§Clinical professor of medicine, Harvard Medical School; physician, Massachusetts General Hospital.

from one hundred and sixty-five to three hundred minutes. The presence of "spasms" or intermittent striking increases in "tone" and changes in the amplitude and frequency of propulsive contractions were assessed by visual inspection of the records. "Tone" during the "spasm"-free intervals was determined by measurement with a centimeter ruler of the distance between the resting level of contractions and the baseline for each tracing. Total contractions (propulsive and nonpropulsive) were determined in three tests by surface-area measurements of the portion of the tracings representing contractile activity. Since the changes in propulsive contractions following the administration of Demerol were striking and could be adequately evaluated by visual inspection, it seemed unnecessary to continue with the surface-area measurements. Changes in nonpropulsive con-

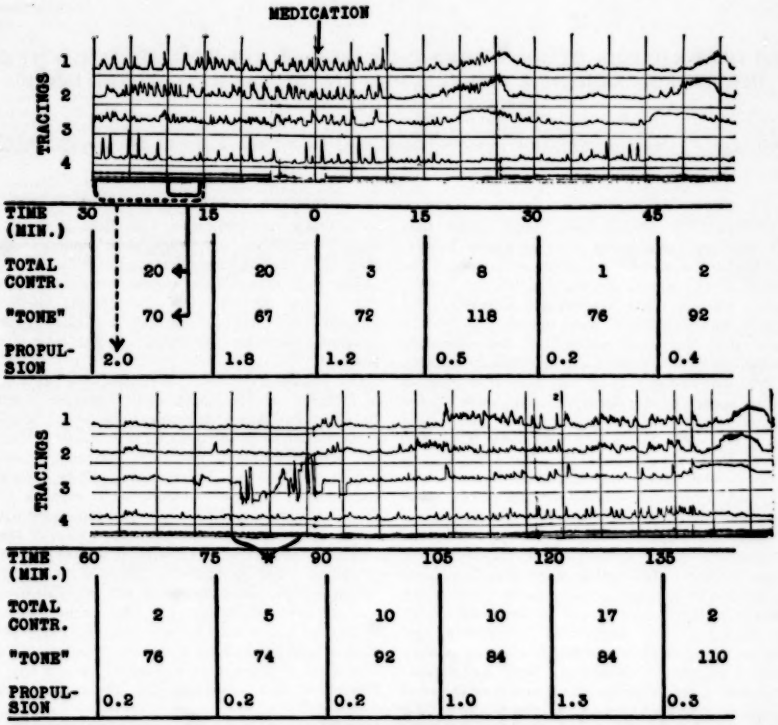

FIGURE 1. *Graphic Record of the Action of 100 Mg. of Demerol Given Subcutaneously on the Motility of Upper Small Intestine.*

The tracings are from the following positions in the upper small intestine: No. 3, from the duodenum; No. 2, from the proximal jejunum or distal duodenum; No. 1, from the proximal jejunum; and No. 4, from the stomach (not used to evaluate effect of drug). The figures below the record indicate changes in motor activity. The values for the levels of total contractions and "tone" represent the mean of the sum of the surface-area measurements of the three intestinal tracings per five-minute period previous to each fifteen-minute interval and are expressed in square centimeters. The levels of propulsive contractions are expressed in arbitrary units and represent the mean of the sum of the values for the three intestinal tracings per fifteen-minute period. The figure shows that Demerol strikingly decreased total and propulsive contractions, causing intermittent "spasms" and a slight over-all increase in "tone." The asterisk represents an artefact in No. 3 tracing.

tractions were difficult to assess even in any quasi-quantitative fashion. With few exceptions, however, changes in their trend could be determined. The same technic and procedures were used for the placebo and morphine tests as for the Demerol studies.[9, 10]

Results

The effect of Demerol on the motility of the upper small intestine was qualitatively similar but quantitatively less marked than that of morphine. Demerol produced fewer "spasms" and caused a less sustained reduction in contractions. A graphic record, illustrative of the changes in motor activity after administration, is shown in Figure 1. The subject, a healthy adult whose test is indicated as No. 5 in Figure 2, was given 100 mg. of Demerol subcutaneously after a sixty-minute control period. Ten minutes later, propulsive contractions (high sustained waves of about one minute's duration) became completely abolished. Within six minutes a "spasm" occurred first in tracing 3 and then in rapid succession in tracings 2 and 1 or over the two more distal areas. During the upstroke and downstroke of the "spasm" a few propulsive and a larger number of nonpropulsive contractions (lower, more rapid waves) appeared, whereas at the height of the "spasm" nonpropulsive waves alone were present. This "spasm" lasted fourteen minutes and was followed by an almost complete disappearance of contractions for the next eighteen minutes. Another "spasm" of about twelve minutes' duration then occurred, followed by minimal contractions for the next forty minutes. At this time propulsive contractions with a few nonpropulsive waves returned partially to the control level for thirty-eight minutes. Another "spasm" of fourteen minutes' duration then appeared, followed by a disappearance of contractile activity for the remainder of the record (not shown in Figure 1). As can be seen in Figure 2, test 5, propulsive contractions appeared again during the last thirty minutes of the four-hour postmedication period although the height of the contractions was 50 per cent less than the average level for the control period. Quantitative estimates of the changes in total contractions, "tone" and propulsive movements are shown by the numbers beneath the

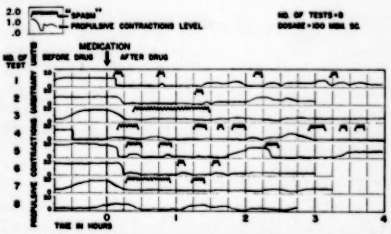

FIGURE 2. *Effect of Demerol on Motility of the Upper Intestine. With the exception of tests 4 and 8 the subcutaneous injection of Demerol, 100 mg., caused a marked decrease in propulsive contractions within fifteen minutes. The maximal effect lasted for about seventy-five minutes, after which contractions returned somewhat but the levels remained well below the average of the forty-five-minute control values. "Spasms" or temporary, sudden increases in "tone" ("saw-toothed" figures) were a frequent occurrence after Demerol injection. The duration of each test is shown by the length of the heavy black lines, which indicate the level of propulsive contractions.*

TABLE 1. *Summary Data of Individual and Mean Values, Showing Percentage Changes in "Tone" during "Spasm"-Free Intervals for Each Thirty-Minute Period after the Subcutaneous Administration of 100 Mg. of Demerol, 10 Mg. of Morphine and Placebos.**

Test No.	Agent Given	Changes in "Tone" after Administration of Agent							
		After 30 min.	After 60 min.	After 90 min.	After 120 min.	After 150 min.	After 180 min.	After 210 min.	After 240 min.
		%	%	%	%	%	%	%	%
2	Demerol	−7	−32	−24	+2	+10	—	—	—
	Morphine	+27	−4	+7	+4	+8	+27	+4	+4
	Placebo	−29	−29	−29	−38	—	—	—	—
3	Demerol	+13	+21	+26	+26	+23	+6	−2	+2
	Morphine	−7	+12	−12	−10	−15	−13	−30	−10
	Placebo	−10	−7	+5	+5	+7	+4	−3	−3
4	Demerol	−6	+12	0	+12	+12	+9	0	+12
	Morphine	−26	−36	−51	−38	−40	−19	−3	0
	Placebo	+21	+38	+28	+71	—	—	—	—
5	Demerol	−2	+15	+10	+28	+30	+8	+15	+18
	Morphine	+9	+2	0	−6	−5	−13	−3	−7
	Placebo	+3	−5	−5	−7	+8	—	—	—
6	Demerol	−7	+7	−16	+1	−5	—	—	—
	Morphine	+1	−8	−4	+2	−7	+6	—	—
	Placebo	0	0	0	−8	−15	−15	—	—
Mean	Demerol	−1	+5	−2	+9	+10	+8	+4	+11
Mean	Morphine	+3	−4	−7	−10	−12	−2	−8	−5
Mean	Placebo	−3	−1	0	+5	−10	−6	−3	−3

*The values for percentage changes in "tone" were determined by division of the average value per thirty-minute period by the average level for the last forty-five minutes of each control period.

graph in Figure 1. These values indicate the striking effect of Demerol on contractile activity as well as the tendency to cause marked elevations in "tone." Between periods of "spasm" "tone" appeared to be slightly above the control levels, as shown by the "tone" measurements in Figure 1 and in Table 1 (test 5). In this subject, therefore, Demerol almost completely abolished propulsive and nonpropulsive contractions and caused intermittent, sudden elevations of "tone" averaging about thirteen minutes in duration. Moreover, during "spasm"-free intervals, "tone" became slightly elevated.

Propulsive Contractions

The effect of Demerol on propulsive contractions is shown individually for the 8 subjects in Figure 2. Except for tests 4 and 8 there was a striking decrease in contractions within fifteen minutes of the injection. For the next seventy-five minutes the

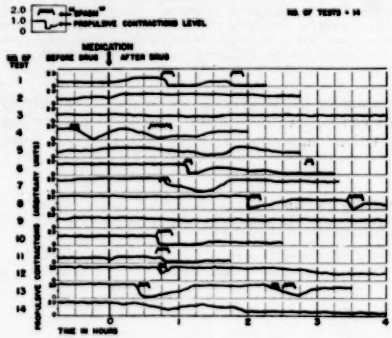

FIGURE 3. *Effect of Placebos on Motility of the Upper Intestine. The spontaneous changes in propulsive contractions and the incidence and duration of "spasms" or temporary, sudden elevations in "tone" following placebo administration are apparent. Tests 2 through 6 represent the placebo studies for the same subjects whose Demerol experiments are numbered 2 through 6 in Figure 2. Each of these subjects had the same test number in both figures. It will be noted that in the placebo studies the occurrence of "spasms" was associated with a marked decrease in propulsive contractions. The reduction in contractile activity lasted for a variable length of time. The incidence of "spasms" was much less after placebo administration than after the injection of Demerol in subjects having both tests.*

contractions remained decreased. Thereafter, activity showed a tendency to increase somewhat, but the level of propulsive contractions remained below the average control levels. The changes in propulsive contractions following the administration of placebos, which have been reported elsewhere,[9] are shown in Figure 3. It can be seen that in these control studies there were considerable variations in contractile activity with the passage of time. The latent period for the decrease in propulsive contractions was both longer and more variable in the placebo than in the Demerol tests. A comparison of a given subject's Demerol and placebo study is shown by tests 2 through 6 in

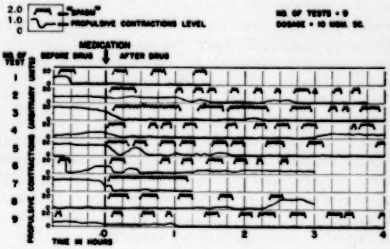

FIGURE 4. *Effect of Morphine on Motility of the Upper Intestine.*

The striking decrease in propulsive contractions and the high incidence of "spasms" or temporary sudden increases in "tone" following the subcutaneous injection of 10 mg. of morphine are illustrated. The subjects having tests 2 through 6 are those whose Demerol and placebo studies are shown in Figures 2 and 3. In all three figures each subject had the same test number. Except for test 2 the drug decreased propulsive contractions within fifteen minutes. In tests 1 and 8 it was difficult to assess the effect on contractions because of the low level of activity during the control periods. The almost immediate occurrence of "spasms" in all tests suggested a partial effect of the drug in every subject.

Figures 2 and 3. Each person has the same test number in both figures. In the subjects with tests 2, 3 and 5 the decline in propulsive activity after the administration of placebos was not marked, whereas in those with tests 4 and 6 the levels of propulsive contractions were more variable, with rather sudden decreases in activity associated with "spasms." The individual changes in propulsive contractions following the subcutaneous administration of 10 mg. of morphine are shown in Figure 4. As reported elsewhere,[10] morphine, with the exception of tests 2 and 8, caused a decrease in contractions within the first fifteen minutes of the injection. In all the tests the initial decline in contractions was associated with the simultaneous occurrence of "spasms," indicated by the "saw-tooth" figures. Except for tests 4 and 8, the falling off in propulsive activity after morphine administration was maintained throughout the period of observation. The subjects who had the morphine tests in addition to the Demerol and placebo studies may be identified by tests 2 through 6 in Figures 2, 3 and 4. Each subject had the same test number in each figure. When the Demerol, placebo and

morphine tests in the same subjects were compared, it was found that although the drugs were equally effective in decreasing propulsive activity for the first one hundred and five minutes, the action of morphine was the more sustained. The one exception was the subject of test 2, who showed a diminution in propulsive contractions fifteen minutes after the injection of Demerol; on the other hand, there was no apparent effect of morphine until the end of the first hour. The comparative action between Demerol and morphine and the changes in propulsive movements after placebo administration are shown in Figure 5. The mean values indicated by the arrows represent in percentages the differences between activity at each fifteen-minute interval after administration and the average level of activity for the last forty-five minutes of the control period. Each test was compared to its own control level. As indicated by the cross-hatched and black arrows, during the first one hundred and five minutes of the post-medication period morphine and Demerol reduced propulsive activity about equally and to a far greater extent than that observed with placebos. Thereafter, the action of morphine was the more sustained of the two drugs. For the one hundred and sixty-five-minute period in which the three groups of studies were compared, the diminution in propulsive contractions after the administration of placebos averaged 9 per cent, with a range of +15 to −28 per cent for any fifteen-minute interval. Demerol decreased contractions on an average of 51 per cent, with a range of −12 to −72 per cent, whereas the average decline in activity after morphine injection was 64 per cent, with a range of −18 to −81 per cent. For the remainder of the observation period the morphine tended to be more effective than Demerol although the reduction in the number of observations during the latter period made the comparison between the two drugs less valid.

The variation in the individual values, typical of the time that the two drugs were maximally effective, is shown by the scattergram in the lower portion of Figure 5. The range of the percentage decrease in propulsive contractions after Demerol was given was −50 to −90 per cent, whereas for the morphine tests the range was −50 to −100 per cent. The variability in the placebo values at this time was +40 to −60 per cent.

Nonpropulsive Contractions

We were unable to evaluate nonpropulsive contractions in terms of quantitative data.[9] As in the morphine studies, after the administration of Demerol nonpropulsive activity changed in the same direction as the propulsive contractions. In the absence of "spasms" they were clearly decreased, and were found to be superimposed on "spasms" after the administration of the drug. During "spasms" nonpropulsive contractions were superimposed on the elevated "tone" levels and at the same time were frequently increased.

"Spasms"

The incidence and duration of "spasms" or the temporary, sustained increase in "tone" is indicated graphically for the Demerol tests in Figure 2 and for the placebo tests in Figure 3.[9] When the two tests in the same subjects (2 through 6) are compared for the first one hundred and twenty minutes of the post-medication period, it can be seen that 10 "spasms" occurred in the Demerol studies and only 2 in the placebo tests. Although the administration of Demerol was therefore associated with a higher incidence of "spasms "than was noted in the placebo tests, the "spasms" were less frequent than when morphine was given. In the same subjects 24 "spasms" occurred during the first two hours after the injection of morphine.[10]

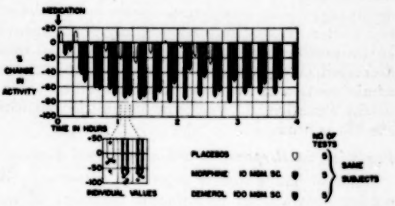

FIGURE 5. *Comparison of the Effects of Demerol, Morphine and Placebos on Propulsive Contractions.*

Both Demerol and morphine decreased propulsive contractions to about the same extent for the first one hundred and five minutes. Thereafter, the action of morphine was the more pronounced. It can be seen that over the one-hundred-and-sixty-five-minute period after administration the effect of the drugs on propulsive activity was much more marked than the spontaneous decline in contractions occurring in the placebo tests. The individual variations for the three groups of studies is shown by the scattergram at the lower portion of the graph. The values for each fifteen-minute period represent the mean of the sum of individual tests, which were compared to the last forty-five minutes of the control period. The duration of each test can be determined from the length of the black lines, which indicate the propulsive contraction levels for subjects 2 through 6 in Figures 2, 3 and 4.

"Tone" Levels during "Spasm"-Free Intervals

The incidence of sudden elevations of "tone" characterized by "spasms" has been discussed. Table 1 shows the summary data of the levels of "tone" during the intervals that were free of "spasms." The average value of each thirty-minute interval after administration has been compared to the mean level of "tone" for the last forty-five minutes of the control period. For the first thirty to one hundred and eighty minutes after the agents were given, the mean "tone" values for Demerol

were increased 6 per cent, with a range of +10 to −2 per cent; the placebo values averaged −2 per cent, with a range of +5 to −10 per cent, and in the morphine tests the mean values averaged −7 per cent, with a range of −2 to −12 per cent. For the remainder of the four-hour observation period, the mean values with Demerol were all increased slightly, and the placebo and morphine tests showed a slight decrease. Thus, when the subjects were considered as a group, Demerol caused a slight but consistent increase in "tone," whereas in the placebo and morphine studies "tone" tended to be unchanged or slightly reduced during the "spasm"-free periods. When the tests were considered individually, there was found to be no consistent trend after the administration of any of the agents. It was possible for "tone" to be increased and then decreased in a given study. In some subjects the administration of the drugs was followed by a consistent elevation of "tone"; in others, the opposite effect was produced.

Variation in Response to Adjacent Bowel Segments

Demerol had a similar depressing effect on propulsive contractions in adjacent segments of the intestine. While "spasms" involved all the areas studied, "tone" during "spasm"-free intervals might be altered in the same or in opposite directions from segment to segment. In these respects the action of Demerol was similar to that of morphine.

Side Effects

Blood pressure, pulse rate and respiration did not seem to be affected by Demerol. The symptoms elicited were minimal. Within the first hour of injection 5 subjects became sleepy, 3 noticed a generalized sensation of warmth, and 1 reported slight dizziness. One subject noted no side effects at all. The side effects of morphine have been reported elsewhere.[10]

Discussion

The effects of the subcutaneous administration of 100 mg. of Demerol on the motility of the upper small intestine in 8 adult subjects have been compared to the action of morphine, 10 mg., given subcutaneously, and to the changes in motility following the administration of placebos. Five of the subjects receiving Demerol were also tested on other days with morphine and with placebos. In the 5 subjects receiving all three agents it was found that Demerol diminished propulsive contractions 12 per cent during the first fifteen minutes. The effect steadily increased until forty-five to sixty minutes after administration, when the maximal decline of 71 per cent in propulsive activity occurred. This maximal effect persisted for the next thirty minutes. Up to this point, the action of Demerol and morphine was similar. Thereafter, propulsive contractions started recovering in the Demerol tests whereas the maximal effect in the morphine studies continued, with only slight recovery through the remainder of the observation period. The magnitude of the decrease in contractions was therefore about the same with the two drugs but less sustained with Demerol. The other difference in the studies was that Demerol produced fewer "spasms" or temporary sudden increases in "tone" than morphine. On the other hand, during "spasm"-free intervals, Demerol appeared to cause a slight but consistent increase in "tone" whereas in the placebo and morphine tests "tone," in the absence of "spasms," was unchanged or tended to be slightly decreased. Although these findings suggested that Demerol caused a more sustained increase in "tone" as contrasted to the more frequent temporary elevations in "tone" noted in the morphine studies, we believed that the differences were not sufficiently striking to establish this point.

So far as the human small intestine was concerned, our findings lead us to agree with those of some previous workers who claim that Demerol decreases contractions in man. Contrary to the observations of Batterman and Himmelsbach,[5] we noted a decline both in segmental or nonpropulsive contractions and in propulsive contractions. The finding of intermittent increases in "tone" or "spasms" is apparently in agreement with the results of dog experiments by Yonkman et al.[6] and Gruber and his associates,[7] which showed that Demerol definitely is capable of stimulating "tone." We were unable to agree with Yonkman's claim that in man Demerol relaxes the smooth muscle of the intestine and morphine acts as a "bowel splint." It seemed to us that both drugs act intermittently as "bowel splints" although this action was more marked with 10 mg. of morphine than with 100 mg. of Demerol given by similar routes. Furthermore, morphine as well as Demerol depressed or arrested motility, if one includes contractile activity in the definition of motility. In this instance, the effect of the two drugs was about the same for the first one hundred and five minutes, with the action of morphine the more sustained thereafter. We are unprepared to say at this time what the clinical implications may be in the observation that morphine acts similarly but with a more pronounced action than Demerol on motor activity of the upper small intestine.

Summary

The effect of the subcutaneous injection of 100 mg. of Demerol on the motility of the upper small intestine in 8 adult subjects is reported. The action of the drug on propulsive contractions, nonpropulsive contractions and "tone" was compared to the effect of the subcutaneous injection of 10 mg. of morphine and to the changes in motility following placebo administration in 5 of the subjects receiving all three agents.

Demerol decreased propulsive and nonpropulsive contractions and caused intermittent "spasms" or sudden elevations of "tone." "Tone" during "spasm"-free intervals tended to be slightly elevated after Demerol administration, and unchanged or slightly decreased in the placebo and morphine tests. Morphine caused a more sustained decrease in propulsive contractions and more frequent "spasms" than Demerol. The effects of the drugs were much more marked than the changes in activity occurring after the administration of placebos.

These findings led us to conclude that the action of Demerol in a dosage of 100 mg. and that of morphine in a dosage of 10 mg. are qualitatively similar. The latter appeared, however, to have a more pronounced action in decreasing contractions and in giving rise to "spasms."

The clinical significance concerning the comparative action of the two drugs on intestinal motor activity remains to be studied.

References

1. Eisleb, O., and Schaumann, O. Dolantin, ein neuartiges Spasmolytikum und Analgetikum (chemisches und pharmakologisches). *Deutsche med. Wchnschr.* 65:967, 1939.
2. Duguid, A. M. E., and Heathcote, R. St. A. Pharmacological action of ethyl methylphenylpiperidinecarboxylate. *Quart. J. Pharm. & Pharmacol.* 13:318-331, 1940.
3. Batterman, R. C. Effectiveness in man of demerol, new analgesic drug. *Federation Proc.* 1:143, 1942.
4. *Idem.* Clinical effectiveness and safety of new synthetic analgesic drug, demerol. *Arch. Int. Med.* 71:345-356, 1943.
5. Batterman, R. C., and Himmelsbach, C. K. Demerol — new synthetic analgesic: review of its present somatics and comparison with morphine. *J. A. M. A.* 122:222-226, 1943.
6. Yonkman, F. F., Noth, P. H., and Hecht, H. H. Demerol: new synthetic analgesic, spasmolytic and sedative agent. I. Pharmacologic studies. *Ann. Int. Med.* 21:7-16, 1944.
7. Gruber, C. M., Hart, E. R., and Gruber, C. M., Jr. Pharmacology and toxicology of ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid (demerol). *J. Pharmacol. & Exper. Therap.* 73:319-334, 1941.
8. Yonkman, F. F. Actions of demerol and morphine on gastrointestinal musculature. *Anesth. & Analg.* 23:207-210, 1944.
9. Chapman, W. P., Rowlands, E. N., Taylor, A., and Jones, C. M. Multiple-balloon-kymograph recording of variations in motility of upper small intestine in man during long observation periods before and after placebo administration. *Gastroenterology* (in press).
10. Rowlands, E. N., Chapman, W. P., Taylor, A., and Jones, C. M. Multiple-balloon-kymograph recording of comparative action of morphine and placebos on motility of upper small intestine in man. *Surg., Gynec. & Obst.* (in press).
11. Chapman, W. P., and Palozzo, W. L., Multiple-balloon-kymograph recording of intestinal motility in man with observations on correlation of tracing patterns with barium movements. *J. Clin. Investigation.* 28:1517-1525, 1949.
12. Chapman, W. P., Rowlands, E. N., and Jones, C. M., Multiple-balloon-kymographic recording of comparative action of oral administration of atropine, tincture of belladonna and placebos on motility of upper small intestine in man. *New Eng. J. Med.* 243:1-8, 1950.

OBSERVATIONS ON THE MANAGEMENT OF HYPERTENSION BY THE KEMPNER RICE DIET*

CHARLES R. WILLIAMSON, M.D.†

FRAMINGHAM, MASSACHUSETTS

KEMPNER'S[1-4] reports of the therapeutic value of a rice and fruit diet in hypertension led to a renewed interest in the dietary treatment of this disorder. Further investigations of the Kempner regimen by other workers have not resulted in any general agreement regarding the beneficial effects.[5-10] The present study has been carried out in an effort to evaluate the effects and possible mechanism of action of the Kempner rice diet.

The great variability of both normal and elevated blood pressures is well known. It is evident, therefore, that in order to establish a particular procedure as responsible for a change in blood pressure, certain criteria must be fulfilled.

In the first place, during a control period when every aspect of management is identical to that of the experimental period except for the experimental procedure, the blood pressure must become stabilized at or above a chosen hypertensive level. How long this control period should be is not entirely clear. Since declines in blood pressure have been observed during the first, second and third weeks of hospitalization with no therapy of any kind, not even bed rest, it is apparent that the control period must be at least three or four weeks.

Secondly, since there is no feasible method of avoiding the powerful psychotherapeutic effect of a bizarre or unusual regimen, if a significant fall in blood pressure occurs, it must be reversible by a procedure that, so far as possible, does not alter the bizarre nature of the regimen as far as the patient is aware.

Methods

Sixty-seven patients with diastolic blood pressures of over 100 were referred for study. The determinations were made by the same two observers in the same arm of the patient in a standard manner. Three to five successive readings were made at approximately half-minute intervals, and the lowest was recorded on each occasion. In general, one pressure was taken in the morning with the patient flat in bed and before his arising; another was taken some time during the afternoon with the patient in a sitting or lying position and after varying conditions of activity. The point at which the

*From the Medical Service, Cushing Veterans Administration Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and the conclusions drawn by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Assistant in medicine, Harvard Medical School; assistant in medicine, Boston City Hospital; formerly, resident in medicine, Cushing Veterans Administration Hospital.

sounds disappeared was taken as the diastolic pressure. All patients were kept ambulatory. They were allowed to leave the hospital for short walks and to attend sports events, and were encouraged to engage in a relatively normal amount of activity, although remaining hospitalized throughout the study.

A control period of at least three weeks, during which the diastolic pressure was constantly above 100, was required prior to the institution of the rice diet.

The diet consisted of 200 gm. of rice (dry weight) with additional calories supplied by fruit, sugar and fruit juices to afford a total of approximately 2500 calories per day. This provided approximately 16.5 gm. of protein and about 5 gm. of fat. The only fluids permitted were the 1000 cc. of fruit juice each day. No sodium chloride was allowed. Daily vitamin supplements and ferrous sulfate were administered. This diet differs from the one used by Kempner only in having a somewhat higher caloric value, achieved by the use of a larger quantity of sugar. Every effort was made to keep the patients strictly on the required diet.

In patients who showed a significant response to this regimen, protein and fat and salt were used to

TABLE 1. *Changes Ascribable to the Rice Diet in 4 Patients Who Exhibited Significant Decrease in Blood Pressure.**

Case No.	Test for Albumin in Urine		Red Cells in Sediment		White Cells in Sediment		Casts in Sediment		Urine Specific Gravity		Serum Nonprotein Nitrogen		Phenolsulfonphthalein Excretion	
	Control	Diet	Control	Diet	Control	Diet	Control	Diet	Control	Diet	Control	Diet	Control	Diet
			per high-power field	per high-power field	per high-power field	per high-power field					mg./100 cc.	mg./100 cc.		
1	++ to ++++	0 to ++++	(Loaded)	10–30	6–10	2–6	Many	None	1.007–1.015	1.010	64–74	33–41	10–13% in 2 hr.	
2	+	+	None	None	25–30	4–8	Rare	None	1.027	1.019	28	32	Normal†	
3	+ to +++	+	Occasional	None	3–5	3–5	Few	None	1.021	1.015	36	34	71% in 2 hr.	
4	0 to +	0 to +	Occasional	Occasional	3–4	3–4	Occasional	None	1.023	1.017	29	32	41% in 1 hr.; 63% in 2 hr.	

*In all patients the heart size, both control and on the diet, was normal.
†26% in 15 min.

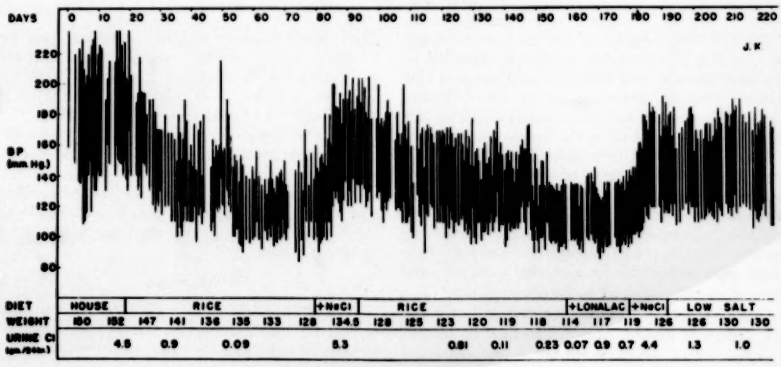

FIGURE 1. *Blood-Pressure Recordings in Case 1.*
It is to be noted that "Lonalac," although containing very little sodium, has an appreciable chloride content; hence the rise in urinary chloride excretion following its use.

supplement the diet during separate periods of study. During one period of twenty-one to twenty-eight days, the addition of 40 gm. of protein and 41.5 gm. of fat (533 calories) was made by the daily administration of 1200 cc. of low-sodium milk

sion to the hospital, these 37 cases might have been recorded as successful therapeutic results.

Among the 30 patients with sustained diastolic hypertension, 3 refused to start the diet, and 7 others were not considered suitable for study be-

TABLE 1 (*Concluded*).

Case No.	Serum Cholesterol		Basal Metabolic Rate		Hemoglobin		Total Protein		Fundi		Electrocardiogram		Body Weight	
	Control mg./100 cc.	Diet mg./100 cc.	Control %	Diet %	Control gm./100 cc.	Diet gm./100 cc.	Control gm./100 cc.	Diet gm./100 cc.	Control grade	Diet grade	Control	Diet	Control lb.	Diet lb.
1	218	127	+2	−25	10.6	12.0	6.0	5.8	IV	I	Left ventricular strain	Improvement	153	117½
2	241	163	+33 and +18	+5	15.8	15.4	7.0	6.7	III	I	Left ventricular strain	Normal	198	170
3	190	124	+1 and −4	−15	16.0	14.4	6.4	6.5	III	I	Normal	Normal	152	139
4	222	150	+17	−6	14.6	14.2	7.2	—	I	I	Left ventricular strain	Digitalis effect	188	168

("Lonalac") containing 15 mg. of sodium. A second group of observations was made during and after a two-week period when 8 to 10 gm. of sodium chloride in capsule form was administered daily. Prior to this period a similar number of identical-appearing capsules of lactose were given for at least a fortnight so that the patients were unaware of the addition of sodium chloride to their regimen.

Observations made in the period preceding the rice diet were repeated after a response of the arterial pressure, after the addition of protein and fat and after the intake of sodium chloride. These studies consisted of determination of basal metabolic rate, electrocardiogram, chest x-ray examination for heart size, funduscopic evaluation and total protein, nonprotein nitrogen, serum chloride, routine urine and blood examinations. Weight was recorded every second day. Twenty-four-hour urinary chlorides were measured weekly to determine adherence to the diet.

RESULTS

Among the 67 hypertensive patients who had been referred because of diastolic pressures above 100, 8 were found to have diastolic values below this level when first seen by us. Fifteen others proved to have highly variable diastolic pressures, which were frequently below 100, and an additional 14 patients exhibited a gradual decline in diastolic pressure to less than 100 during the control period of three weeks. Thus, 37 of the 67 patients were unsuitable for special dietary study because they "improved" during the control period. Had the rice diet been instituted immediately upon admis-

cause of complications such as severe retention of nonprotein nitrogen, congestive heart failure and serious cerebrovascular disease.

The 20 remaining patients were placed on the strict rice diet. Seven refused to co-operate after

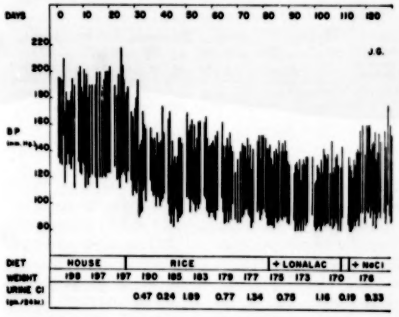

FIGURE 2. *Blood-Pressure Recordings in Case 2.*

intervals of one to four weeks, and observations were discontinued. One had rapid loss of weight of such severity that the diet was altered. An additional patient, who had nitrogen retention at the start of the diet, showed a rising nonprotein nitrogen early in the diet period, and salt restriction was therefore discontinued.

It was thus possible to carry out extended observations on 11 of the original 67 patients. Each of the 11 remained on the rice diet for six or more weeks. All described some symptomatic improvement, such as disappearance of headaches, lessening of emotional tension, clearing of vision, and increased sense of well-being. In every case there was a steady loss of weight during the rice-diet period. Seven of the 11 patients demonstrated no significant change in diastolic pressure. Four exhibited the reductions in diastolic pressure indicated in Figures 1-4. In this group the 3 having retinopathy showed marked improvement (Table 1). Two of the 4 had reduction in albuminuria. Two of the 3 patients with abnormal electrocardiographic curves exhibited more normal tracings after the reduction in blood pressure. The basal metabolic rate and serum cholesterol decreased in all 4 cases.

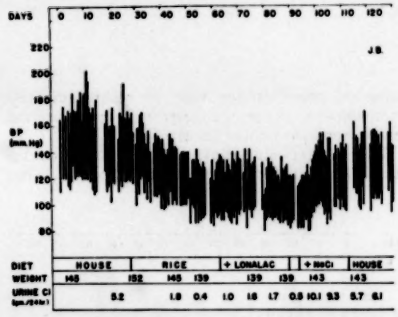

FIGURE 3. *Blood-Pressure Recordings in Case 3.*

The nonprotein nitrogen dropped in the case in which it had initially been moderately elevated.

It is thus apparent that 4 of the 11 patients with diastolic blood pressures of 100 or more sustained for a minimum period of three weeks in the hospital showed significant improvement while partaking of the strict rice diet. This improvement might have been coincidental, due to the psychotherapeutic effect of the bizarre diet or due to some specific feature of the diet such as protein deficiency or salt deprivation.

During the period when additional salt-free protein was given as "Lonalac" to 3 of the 4 patients, no change in blood pressure or symptomatology occurred. The addition of 8 to 10 gm. of sodium chloride to the daily diet was followed by a significant increase in diastolic pressure within a week in 1 of the 4 patients. In this case withdrawal of salt was followed by a return of the blood pressure to its previous low level. A second addition of salt once again was accompanied by a significant rise. Two of the remaining 3 patients exhibited average rises of 9.7 and 16.0 in systolic blood pressure after the administration of salt. The fourth

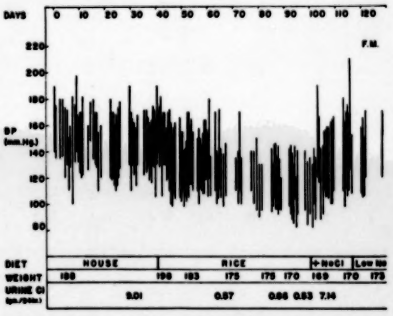

FIGURE 4. *Blood-Pressure Recordings in Case 4.*

patient showed no significant change in diastolic pressure.

CASE REPORTS

CASE 1 (C. V. A. H. 6837). J. K., a 38-year-old man, was admitted to the Medical Service on November 17, 1947. He had been in good health until 6 months before admission, when he first noted the gradual onset of dimness of vision and occipital headaches. His vision progressively diminished until he was unable to read even large type, and the headaches became generalized and so severe as to be incapacitating. Ten days before admission for the first time he consulted a physician, who advised immediate hospitalization.

Physical examination revealed a well developed and well nourished man who appeared chronically ill. Vision was markedly diminished, especially in the left eye. The fundi showed tortuosity of the arterioles, arteriovenous nicking, considerable areas of exudate and fresh hemorrhage, and papilledema bilaterally. The findings were most marked in the left fundus. The retinas appeared swollen and waxy. The peripheral vessels felt moderately sclerotic.

The blood pressure was 260/160.

The urine gave a ++ to ++++ test for albumin repeatedly; the urinary sediment was loaded with red blood cells and contained 10 to 15 white blood cells per high-power field, as well as many granular casts. The specific gravity varied between 1.007 and 1.015. There was only 10 per cent phenolsulfonphthalein excretion in 2 hours. Examination of the blood disclosed a red-cell count of 3,950,000, with a hemoglobin of 11.0 gm. per 100 cc. There was evidence of left ventricular strain by electrocardiogram. The nonprotein nitrogen was 64 mg. per 100 cc.

During the first 4 weeks of hospitalization, he had continued, intense headaches and nausea, and he vomited almost daily. Sedatives and narcotics were only partially effective in controlling his discomfort. He became almost completely blind on the 4th hospital day, after a reaction to the dye during intravenous pyelography.

With the fall in blood pressure, coincident with diet therapy, there was return of vision and disappearance of headache, the fundi changed from Grade IV to Grade I, there was im-

provement in the urinary abnormalities except for the specific gravity, and the nonprotein nitrogen fell to normal values. Coincident with salt administration on each occasion, the headache returned, low backache developed, and fresh hemorrhages appeared in the fundi. During the second period of lowered blood pressure, he had three typical anginal attacks. After the second episode of salt administration, he was placed on a somewhat more liberal diet. There was gradual increase in nonprotein nitrogen in the subsequent months. He died of uremia 5 months after completion of study. At post-mortem examination the kidneys showed chronic glomerulonephritis. The renal arterioles were markedly hyalinized and narrowed. In addition, there was an old thrombus in the circumflex coronary artery.

Case 2 (C. V. A. H. 8358). J. G., a 48-year-old World War I veteran, was admitted to the Medical Service on February 20, 1948, with the complaint of headaches and dizzy spells of 6 years' duration. The patient was rejected by his Selective-Service board in 1942 because of "high blood pressure and something in the urine." Shortly after this, severe frontal headaches, usually occurring daily and lasting for several hours, first developed. In addition, he had frequent episodes of dizziness and lightheadedness. For several years he had also noted abnormal exertional dyspnea on climbing one flight of stairs. There had been no chest pain, ankle edema, visual disturbances or paroxysmal nocturnal dyspnea.

Physical examination disclosed a moderately obese man with a blood pressure of 200/135; the fundi showed Grade III hypertensive retinopathy, with arteriovenous nicking, tortuosity and flame-shaped hemorrhages. Dupuytren's contractures were present bilaterally. The remainder of the physical examination was within normal limits. The urine gave a + test for albumin, with occasional white cells in the sediment. Routine examination of the blood, an intravenous pyelogram, the total protein and the nonprotein nitrogen were within normal limits. An electrocardiogram demonstrated a pattern of left ventricular strain.

The patient became asymptomatic during the control period. Coincident with the fall in blood pressure, which occurred while he was partaking of the rice diet, the retinal hemorrhages disappeared, and the electrocardiogram returned to normal.

Case 3 (C. V. A. H. 8650). J. B., a 39-year-old man, was admitted to the Medical Service on March 12, 1948, with the complaints of headaches, nausea, vomiting and high blood pressure. The present illness had begun in 1932, when the patient, who was then in the Army, noted headaches and nausea and was found to have albuminuria. Shortly thereafter he was discharged with a diagnosis of chronic nephritis. During the following 15 years a gradually progressing hypertension was noted by his physician. In addition, during 1935, 1938 and 1939, the patient had brief recurrences of headaches, nausea and vomiting lasting several days. From 1940 to 1947 these attacks became gradually more frequent until they were preventing him from working several days a week. From December, 1947, to the time of admission, the patient had almost daily attacks of severe headache and vomiting.

On physical examination the fundi showed arteriovenous nicking, narrowing and tortuosity of the vessels and two small hemorrhages on the right.

The remainder of the physical examination was within normal limits.

The blood pressure was 204/130.

The urine gave a + test for albumin, with occasional white and red blood cells and hyaline casts in the sediment. Routine examination of the blood, an electrocardiogram, an intravenous pyelogram, the total protein and the nonprotein nitrogen were within normal limits. The phenolsulfonphthalein excretion was 30 per cent in 15 minutes and 71 per cent in 2 hours. During the 1st month of observation, the patient complained almost daily of intense, incapacitating headaches accompanied by nausea and occasional vomiting. Histamine and benzodioxane tests caused insignificant changes in the blood pressure.

Coincident with the fall in blood pressure while on the rice regimen, the patient became asymptomatic, urinary albumin diminished, and the retinal hemorrhages cleared.

Case 4 (C. V. A. H. 10275). F. M., a 47-year-old man, with hypertension of 4 years' duration, was admitted to the hospital on June 7, 1948, because of exertional dyspnea and several episodes of paroxysmal nocturnal orthopnea during the previous month. There was a period during 1945 when he had had moderately severe occipital headaches and mild dizziness. During the year before admission, nocturia and urinary frequency had been bothersome symptoms. One year before admission for a few days he allegedly had a paralysis of the right facial nerve and a staggering gait.

Physical examination showed a well developed, slightly obese, quite nervous man, who did not appear ill. The fundi revealed minimal hypertensive vascular changes. The heart was not enlarged and exhibited no murmurs, and the rhythm was regular. The lungs were clear; the vital capacity was 3400 cc. No peripheral edema was present.

The pulse was 100, and the blood pressure was 190/140.

The urine had a specific gravity of 1.023 and showed a constant + test for albumin, with a normal sediment. The hemoglobin was 14.6 gm. per 100 cc. The nonprotein nitrogen was 29 mg. per 100 cc. Phenolsulfonphthalein excretion was 17 per cent in 15 minutes and 63 per cent total in 2 hours. An electrocardiogram showed a pattern of left ventricular strain. The heart size was at the upper limit of normal on x-ray examination. The kidneys were normal by intravenous pyelography.

Unfortunately, in the 5th hospital week and before the onset of rice diet, the patient had a vascular accident in the cerebellum and concomitantly suffered acute congestive heart failure. He was given digitoxin on the day the rice diet was begun. He rapidly regained compensation, but unsteadiness of gait persisted. The blood pressure remained unchanged for 1 week after these events.

No significant symptomatic changes occurred while he was on the rice regimen.

Summary

Observations on 67 patients with diastolic blood pressures of above 100 are reported. In 37 of these, diastolic hypertension was not sustained during a control period of three weeks.

Ten of the 30 patients with sustained diastolic hypertension were not placed on the rice diet either because of unwillingness to start the regime or because of the presence of severe complications.

Eleven of the 20 patients placed on the rice diet followed the regime for six or more weeks. Four of these demonstrated a significant decrease in diastolic blood pressure.

The addition of salt-free protein and fat to the diets of 3 of these patients did not result in any change in blood pressure or symptomatology. The administration of sodium chloride without the knowledge of the patients was followed by a rise in systolic blood pressure of more than 20 in 1 of the 4 cases and equivocal rises in 2 others. It thus appears that sodium chloride restriction may play a significant role in these results.

The relation of malnutrition and of the psychotherapeutic effect of such a bizarre regime must be considered.

I am indebted to Dr. Maurice B. Strauss for his advice and continuous interest in this project and to Miss Elsie C. Rossmeisl for technical assistance.

References

1. Kempner, W. Treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M. J.* 5:125-133, and 273, 1944.
2. *Idem.* Compensation of renal metabolic dysfunction: treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M. J.* 6:61-87 and 117-161, 1945.

3. *Idem.* Some effects of rice diet treatment of kidney disease and hypertension. *Bull. New York Acad. Med.* 7:358-370, 1946.

4. *Idem.* Treatment of hypertensive vascular disease with rice diet. *Am. J. Med.* 4:545-577, 1948.

5. Flipse, M. E., and Flipse, J. J. Observations in treatment of hypertension with rice-fruit diet. *South. M. J.* 40:721-728, 1947.

6. Schroeder, H. A., Futcher, P. H., and Goldman, M. L. Effects of diet of rice and fruit juices upon blood pressure of hypertensive individuals. *J. Lab. & Clin. Med.* 32:1509, 1947.

7. Perera, G. A., and Blood, D. W. Relationship of sodium chloride to hypertension. *J. Clin. Investigation* 26:1109-1118, 1947.

8. Contratto, A. W., and Rogers, M. B. Use of rice diet in treatment of hypertension in nonhospitalized patients. *New Eng. J. Med.* 239:531-536, 1948.

9. Rosenberg, B., Rosenthal, A. E., and Rosenbluth, M. B. Effect of low sodium diet and rice diet on arterial blood pressure. *Am. J. Med.* 5:815-820, 1948.

10. Schroeder, H. A., Goldman, M. L., Futcher, P. H., and Hunter, M. Low sodium chloride diets in hypertension: effects on blood pressure. *J. A. M. A.* 140:458-463, 1949.

MEDICAL ASPECTS OF CIVILIAN DEFENSE

CHARLES H. BRADFORD, M.D.*

BOSTON

DOCTORS have never played a tactical part in war. Even in the recent conflict, in which casualties were heavy, the medical profession did vastly more to lighten the load of human suffering than to strengthen the nation's fighting arm. As one studies the outlook of the future, it may well be shown that doctors will carry on one of the most vital parts in the defense of the nation under circumstances that will be extraordinarily different from the past. Yet they tend to be so absorbed in the scientific interests of their profession that few give serious thought to the nature of the military crisis that threatens, and still fewer take the time to consider the need of plans for meeting the immense burden that may suddenly be thrown upon them. A brief survey of these subjects will convince any thinking observer of the following points.

Despite possibilities of an unexpected emergency catastrophic in its proportions, the plans of medical mobilization are still based on the cumbersome, antiquated and outmoded system of procurement and selective service. Notwithstanding knowledge of the effects of atomic bombs in war, no steps have been taken to provide hospital facilities or ambulance services, or medical supplies or basic equipment in anything like the proportion to the number of casualties that can be predicted with certainty in case of an attack on one of the large cities. Likewise, no staff personnel for manning such hospitals, not only with doctors but also with nurses, orderlies and aides, have been made available. Plans for medical mobilization have been prepared in many states; but even the best of them are inadequate and this at a time when every news release shows the threat of full-scale war to be more urgent, more imminent and more harrowing than ever before.

To overcome this attitude of indifference, the medical profession should be awakened to certain realities. Physicians should first realize that warfare has undergone such revolutionary changes that none of the strategic patterns familiar throughout the past bear any resemblance to the methods that may develop in the near future. A few of the circumstances responsible for the change bear enumeration. One must accept the fact, hard to believe, that the speed of attack has now exceeded that of sound. In the Civil War, an army's advance was limited to the speed of a galloping horse. In World War I, the airplane reached a combat speed of about 200 miles an hour. In World War II, combat planes flew more than twice as fast as this, and the Germans introduced a very few jet planes three times as fast. Today, supersonic speed is a reality, and tomorrow it will be commonplace.

As the speed of attack changes, so does its range. General Kenney has recently stated that with the fleet of bombers now in mass production in Russia, every American city is subject to attack from Russian airports. This change of speed and range has modified the strategic concept of armies meeting on fields of battle, and has transferred the center of attack from distant outposts to the nation's industrial centers. Cities are now *at the front*, tactically speaking. This fact is even more accentuated by the possibilities of guided atomic missiles capable of long flights under accurate control. With such weapons, the maneuvers of armies, as history has known them, suddenly become obsolete, and warfare is transformed into a contest of civilian and industrial survival under conditions of widespread devastation.

It must also be realized that the oceans, which have always afforded lines of reinforcement and supply, may now be almost completely closed to shipping in times of war. This results from the effectiveness of submarine and air attack. Convoys of ships will be unable to move, and expeditionary forces will be obliged to stay at home. The navies themselves have gone beneath the surface, and their movements can only be traced by relatively ineffective radar detection. Their striking power, however, will penetrate farther than ever before because of their ability to rise suddenly and launch guided missiles with atomic bombheads.

Although a survey of military and naval tactics such as this hardly belongs in a medical article, it serves as a necessary background to help one understand the nature of the medical emergency that

*Assistant professor of orthopedics, Boston University School of Medicine; member, orthopedic staff, Boston City Hospital and Mount Auburn Hospital, Cambridge.

would develop under war conditions. One other fact requires mention. In the past, war has been governed by traditions of international law that both sides respected to some extent. International law no longer exists today except as a handicap to the initiative of the free, civilized nations. War, if it comes, will not begin with any ultimatum or declaration of hostilities. It is more likely to open with mushrooming columns of atomic smoke over one or more American cities. After such an attack, the words *total war* may gain a significance never before conceived or imagined, and may include gas and bacterial attacks as well as the expected atomic bombs and their resulting radioactive devastation. This, then, is the kind of war that may be expected, if war should come.

The principal interest of doctors is the medical problem of civilian defense, which can be comprehended more clearly if the number of casualties expected can be estimated. Two years ago an official agency predicted that any urban area with a dense population would yield at least 100,000 casualties, of which 60,000 would be seriously wounded and 40,000 would be dead or dying. Since then, introduction of hydrogen bombs has greatly increased this estimate, but of course no specific figure can be offered. It is enough to appreciate the fact that casualties beyond any proportion previously known may occur in one, several or many American industrial centers. Under the pattern of bombing carried out by the Allied air forces over German cities in the past war, many larger centers were completely obliterated, and *every* major city suffered over 40 per cent destruction — and this *without* atomic bombs. If another war comes, when atomic bombs will almost certainly be used, American cities must expect corresponding devastation. It must also be remembered that the destruction of the cities will entail wholesale loss of their hospital facilities. A bomb centered over Copley Square in Boston, for instance, would certainly render ineffective the City Hospital, the New England Medical Center, the Massachusetts Memorial Hospitals, and the Peter Bent Brigham, the New England Baptist and Deaconess, the Children's, the Beth Israel and the Massachusetts General hospitals, as well as all the smaller hospitals in between — to say nothing of the possibility of including the Carney, St. Margaret's, St. Elizabeth's, Marine, Mount Auburn and Cambridge City hospitals, all of which lie within dangerous distance of the target area.

In the face of imminent danger, the most futile policy men can adopt is to sit by idly and hope that it may never materialize. Without by any means abandoning hope, they should not fail to prepare measures for defense suited to the emergency that threatens. The more the character of these dangers is studied, the more one realizes that the medical profession will bear a great burden of responsibility. Medicine will no longer function as an auxiliary of the other services but as a primary department of itself. There is not space here to present any detailed plans, but it seems worth while to offer some thoughts on the formation of a structural plan or policy around which details may develop.

No progress can be made until it is realized that for a future emergency enlistment of medical services in the Army and Navy as practiced in previous wars, and as now established, is so completely wrong that it would paralyze any effective plan for civilian defense. This statement may seem categorical, but it can easily be substantiated. In high-speed, atomic warfare, the deployment of doctors and hospital facilities must follow the concentration of casualties, and this will change from armies waiting for action at imaginary fronts, to the industrial centers where actual devastation is likely to occur. The early part of World War II demonstrated this in Britain, where the soldiers at their invasion posts were the safest members of the population, whereas their families, left behind in British cities, bore the brunt of the blitz. In future warfare, there is likely to be no combat zone of any magnitude except for civilian target areas of economic importance, where populations are heavily concentrated and where the number of casualties may be immense. Thus, the number of doctors needed will be very much greater than ever before, and the waste of doctors, improvidently squandered throughout military and naval establishments, idly waiting for action, will be not only inexcusable but insupportable.

As a further point concerning the use of doctors in the armed forces, it should be observed that instead of profiting by the acknowledged needs of unification, the medical corps has been divided still further through the creation of a separate air corps. Thus, there is now an Army medical corps separate from the Navy and separate again from the Air Corps, each independent of the other, and duplicating the services of the other, and no one of the three adapted to the care of civilian casualties. Intelligent men will not need arguments to persuade them that this system is altogether wrong in its concept. In fact the first and most constructive step in the planning of a sound medical defense would be to abolish the medical services of Army and Navy and Air Force altogether and to combine their staffs under a unified medical service whose chief should be directly subordinate to the Secretary of Defense. To be effective, such a department must operate without the blundering interference or control from other services, and without the stupid mismanagement of line officers. Such a department of medical defense should be ready to treat all sick calls and all casualties, whether civilian, Army, Navy or Air Force, in the same hospitals and by the same organizations.

This was effectively practiced in Britain during the blitz on a reasonably large scale, and the feasibility of such a scheme is fully established.

No matter how the military medical services operated, the great bulk of casualties in another war would require treatment at the hands of civilian organizations. If such an emergency comes, the demands will be so pressing that no time can be allowed for preparation. As individuals or even in small teams or separate hospitals, doctors could accomplish almost nothing. On the other hand, if preliminary plans are made and a civilian medical organization is ready, very great relief can be carried out. The same problem confronted Britain in 1938-39, when the possibilities of air attack were faced, and the people very wisely adopted laws that proved adequate in the crisis. They created an emergency medical service under a council and director with dictatorial powers. At the onset of war, all doctors were subject to the orders of this service, and private practice virtually ceased. In the civilian medical framework in the United States today, through state medical societies and district subdivisions, a similar plan, capable of immediate activation could, without great innovation, be created. Each district, under a committee of its own, could form its plans for the emergency, and its members could be assigned in advance to cadres forming portable hospitals, field hospitals and general hospitals. Such a state-wide organization would be potentially mobile, so that if one city were devastated, the neighboring localities could rush surgical teams to the scene of attack, and, at the same time, evacuation of less severely wounded persons could proceed in the other direction.

Such an organization would require the disciplined regulation of a legally constituted director and an administrative staff, who could be given authority in advance through recommendations by the medical society and action of the legislature. If copied in other states, these organizations could be prepared for federal control, like the National Guard, whenever summoned into action. The national department of civilian defense could then take them over and direct their efforts.

It is clear that medical staffs cannot operate without hospital facilities and equipment. If a plan of this nature were adopted, each unit would require a base for its activities, as well as the instruments and drugs necessary for its work. The hospital problem could be handled by the assignment of each unit to some existing institution that could be quickly transformed for this purpose, such as boarding schools and colleges. Similarly, each unit would need its administrative staff, ambulance service and nursing corps, for which personnel would have to be recruited in advance. Portable hospitals or mobile surgical hospitals of a size smaller than general hospitals could be centered around assembly points in the suburbs, which would provide housing for headquarters, such as high schools and armories. They could be assigned tentage, cots and a train of trucks, together with mobile x-ray and operating-room equipment such as was used for hospitals of this type during the war. The cities themselves would have to be districted off for aid stations, ambulance stops and evacuation posts where the wounded could be gathered and sorted.

Several topics of greater importance than details of planning require mention. The first is the fact that immediate attention should be given to the question of hospitalization in the large cities. Every effort should be made to preserve a ring of available hospitals at a radius of 15 to 35 or 40 miles around each city. To meet this purpose in Boston, for instance, the Army or Veterans Administration hospitals at Ft. Devens, Framingham, Waltham and West Roxbury should be available. Despite economies that might be gained from the closing down of some of these institutions, their value in case of emergency should be remembered. Furthermore, when new hospitals are built, they should be established somewhere on the periphery, and not in an urban center. Decentralization will be the keynote of defense.

To meet the need for supplies, a central medical organization would be required, with a number of large depots where great reserve quantities of drugs, plasma, surgical materials and other necessary equipment could be stored. These should be supplemented by an interlocking system of blood banks and laboratories. During the past war there was an acute shortage of surgical instruments, which could not be obtained on short notice, and there was a threatened shortage of digitalis and other vital drugs. Provisions should be made far enough ahead to prevent similar serious shortages. Special committees of hospital administrators and of executives of medical-supply houses should supervise this part of the planning. Similarly, a special committee should supervise plans for transportation facilities, since the entire service will depend on this for movement of patients as well as supplies. Among other special committees would be the important one for nursing and one for hospital aides, who might be called upon to carry the greatest part of the nursing function.

Still a third aspect of defense would be the public-health menace. Sewage systems would be wrecked by bombs, and water contamination, food shortages, and epidemics would have to be anticipated. The entire civilian population would need immunization against tetanus, typhoid and other diseases. They should also receive blood typing, and identification tags should be issued and stamped. Tattooing, perhaps, would be preferable, judging by the Army's experience with tags. Widespread instruction would be required in sterilization or chlorination of water and in sanitary measures effective

during disasters. All these matters, however, could safely be left to the expert planning of the very competent state public-health departments, with the aid, perhaps, of the department of education.

It would be tedious to pursue this great project of planning defense through all its ramifications. The obstacle is the basic belief that "It won't ever happen to us."

Since this article was first prepared, it has already happened in Korea, and we hardly know on what front to expect the next assault. Although hysteria should be avoided, we must also avoid complacency or delay.

"The affair cries, Haste and Speed must answer it!"

520 Commonwealth Avenue

AUREOMYCIN IN THE TREATMENT OF AMEBIASIS*

C. F. Gutch, M.D.†

LINCOLN, NEBRASKA

IN THE long-continued search for amebicidal agents applicable to treatment of human infestations by *Endamoeba histolytica*, attention in the past year has been drawn to the apparent effectiveness of aureomycin. At the Veterans Administration Hospital in Lincoln, Nebraska, 20 patients with proved amebiasis have received aureomycin, and the results are believed to confirm those of other workers.

The 20 patients so treated at Veterans Administration Hospital, Lincoln, presented the usual variety of symptoms and physical findings. Four had suggestive impairment of liver function. Four others had narrowing or deformity of the cecum consistent with amebic typhlitis by x-ray study. No ulcerative lesions were demonstrable on proctosigmoidoscopy.

Table 1. *Effect of Aureomycin on Cases of Amebiasis.*

	Case No.	Age	Parasite Intensity in Initial Stools	Aureomycin Dosage	Side Effects	No. of Stool Series*	Period of Observation
		yr.		gm.			
1		54	++	8.0	None	5	5 mo.
2		60	+++	8.0	None	6	5 mo.
3		31	++++	8.0	None	7	5 mo.
4		29	+++	17.5	Giddiness	4	3 mo.
5		58	++++	20.0	None	9	5 mo.
6		24	++	14.75	None	4	3 mo.
7		33	+++	20.0	Slight diarrhea	7	3 mo.
8		22	++	20.0	None	7	3 mo.
9		28	+++	20.0	None	8	4 mo.
10		24	++	20.0	None	8	5 mo.
11		52	++	20.0	Pruritus	6	3 mo.
12		53	++	20.0	Slight headache	12	4 mo.†
13		25	++++	20.0	None	3	3 mo.
14		26	+	20.0	None	5	3 mo.
15		40	+	12.0	None	2	1 mo.
16		28	+	21.0	None	4	2 mo.‡
17		20	++++	28.0	Giddiness	4	3 mo.
18		53	++	20.0	None	4	3 mo.
19		23	++++	12.0	None	2	1 wk.
20		25	+++	12.0	None	2	1 wk.

*A series of stools indicates three liquid stool specimens obtained after preparation of the patients with cholphenolate and Phospho-Soda.

†Stools positive at 6 weeks; patient received 28 gm. in second course; four stool series up to 2 months later negative.

‡Stools positive at 6 weeks; patient given 12 gm. in second course; two stool series negative up to 10 days later.

The pertinent data in these cases are shown in Table 1. Aureomycin was given orally in divided doses of 0.75 to 1.0 gm. every six hours for a total of 8 to 28 gm. The first patients treated received only 8 gm. each. Later, the dosage was increased to 20 to 28 gm., which has since been reduced, to determine, if possible, a minimum dosage level. Side effects were minimal, and in no case was it necessary to discontinue medication. Slight nausea, giddiness and headache increased in frequency as the total dose was increased. Slight pruritus ani developed in 2 patients four to six weeks after treatment.

McVay, Laird and Sprunt[1] and Fuller and Faust[2] first reported the apparent inhibitory action of aureomycin upon *E. histolytica* in vitro. McVay and his colleagues, Most[3] and, more recently, Hughes[4] administered aureomycin to patients with amebiasis and reported significant percentages of subsequently negative stool studies.

*From the Department of Internal Medicine, United States Veterans Administration Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and the conclusions drawn by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Resident in internal medicine, United States Veterans Administration Hospital.

Symptomatic relief was prompt in all cases. All patients with initial roentgenologic changes in the colon were re-examined after six weeks, and disappearance of the deformity was found. Also, after completion of aureomycin therapy, the stool specimens did not contain macrophages, epithelial cells and cellular débris, which are frequently noted after other treatment.

All patients had negative stool examinations at the termination of therapy. The examinations were repeatedly negative in 5 cases up to five months later and in 10 others three months after treatment. Two patients were found to have heavy infestations of trophozoites at their six-week checkup. Both were given a second course, and in the first case five examinations of the stools up to two months later were negative. The more recent case had two negative series up to ten days after the second course.

What constitutes a proper follow-up period after any therapy for amebiasis depends upon the criterion taken for "cure." Most authorities[6] require repeated negative stool examinations for six to twenty-four months. Review of cases treated at this hospital previously indicated positive stools were most often found within three to five months of treatment, when recurrence took place. Experience with other amebicidal agents (carbarsone, chiniofon, Vioform, Diodoquin and emetine) indicated a recurrence rate of 11.5 per cent within five months,[6] the majority appearing within three months. Thus far, results of the aureomycin therapy appear to compare with best conventional treatment. Serious toxic effects of aureomycin are apparently minimal. No evidence of toxicity in the myocardium, marrow, liver or kidney was observed.[7] This statement cannot be made of emetine or the organic arsenicals.

Summary

Twenty cases of amebiasis treated with aureomycin at the Veterans Administration Hospital in Lincoln, Nebraska, are discussed. All stools were negative for *Endamoeba histolytica* at the end of treatment. Fifteen patients have had repeatedly negative examinations three months or longer after treatment.

Two were found to have reappearance of active infestations after six weeks. After a second course of aureomycin both again had negative stool examinations, and 1 continued so after two months.

The recurrence rate after aureomycin appears to compare with that after other therapeutic routines for amebiasis.

Lack of serious toxicity is believed to make aureomycin a desirable agent in the treatment of amebiasis.

References

1. McVay, L. V., Laird, R. L., and Spruit, D. H. Preliminary report of successful treatment of amebiasis with aureomycin. *Science* **109**:590, 1949.
2. Fuller, F. W., and Faust, E. C. Aureomycin in cultivation of *Endamoeba histolytica*. *Science* **110**:507, 1949.
3. Most, H. Recent advances in therapy of more common protozoan and helminthic infections of man. *Bull. New York Acad. Med.* **25**: 717-740, 1949.
4. Hughes, J. D. Treatment of amebiasis with aureomycin. *J. A. M. A.* **142**:1052-1054, 1950.
5. Elsom, K. A. Amebiasis, with especial reference to its late complications. *Veterans Admin. Tech. Bull.* (T.B. 10-27), April 12, 1947.
6. Zinneman, H. H., and Gutch, C. F. Unpublished data.
7. Harvey, J. C., Mirick, G. S., and Schaub, I. G. Clinical experience with aureomycin. *J. Clin. Investigation* **28**:987-991, 1949.

MEDICAL PROGRESS

VITAMIN B_{12} AND PERNICIOUS ANEMIA*

MAURICE B. STRAUSS, M.D.†

FRAMINGHAM, MASSACHUSETTS

TO THE microbiologist, vitamin B_{12} is one of the newest of the growth factors necessary for certain bacteria. To the biochemist, it appears to afford new information concerning nucleic acid synthesis. To the poultry scientist it represents a further step in the elucidation of the nature of the factors necessary for the best hatchability of hens' eggs and the growth of chicks. To the physician, vitamin B_{12} appears to be the long-sought antipernicious-anemia principle of liver, and to afford new insight concerning the pathogenesis of a disorder that has fascinated medical men since its original description by Thomas Addison a century ago.

Since interest in the newest member of the vitamins stems from its significance in pernicious anemia it may be well to review certain aspects of this malady. No endeavor is made to cover all the facets of this disease, which are completely discussed in readily available textbooks and monographs.

CLINICAL ASPECTS

Pernicious anemia is a deficiency disease due to the failure to assimilate essential material from food. It is manifested as a macrocytic anemia associated with disturbances of the gastrointestinal tract and frequently of the nervous system. Untreated, the disease progresses over a period generally of about three years to a fatal termination. Under adequate treatment the blood becomes essentially normal, digestive symptoms vanish and manifestations referable to the nervous system are completely arrested. The disease occurs particularly in the fourth and fifth decades of life, although rare cases have been reported before the age of thirty. It is most common in blue-eyed persons of northern European stock, but typical cases have occurred in essentially every race, including the Negro. A familial tendency is common. The onset of the disease is usually insidious, and all too frequently gastrointestinal, neurologic or cardiac symptoms precede the development of obvious anemia by many months. Every patient of middle age or over who complains of indigestion, flatulence, anorexia, "gall-bladder attacks," diarrhea or soreness of the tongue should have the diagnosis of pernicious anemia excluded. A "beefy," "inflamed" or pale, smooth tongue, although found in other deficiency disorders, should always arouse the suspicion of pernicious anemia. Any patient with persistent paresthesias of the hands or feet together with anemia should be considered to have pernicious anemia until proved otherwise. The numbness and tingling of the extremities in pernicious anemia differ from those encountered in many other severe anemias and in circulatory disturbances in being relatively constant over long periods. Other manifestations of the neural changes of pernicious anemia may suggest "neuritis," tabes dorsalis, fallen arches or "rheumatism." Gross diminution of ability to perceive the vibration of a tuning fork held in contact with the tibia is an almost constant finding in the presence of the neural lesion of pernicious anemia. Reflex changes vary from complete absence to extreme hyperactivity associated with clonus, depending on whether the lesion is predominantly in the posterior or lateral columns of the spinal cord. In the former, ataxia and a positive Romberg sign occur, and in the latter, spasticity and the sign of Babinski. Any combination of signs in the posterior and lateral columns may be seen. However, pupillary abnormalities and changes in pain, light-touch and thermal sensitivity probably never occur unless there is associated polyneuritis. Sphincter disturbances are common in advanced cases. In the absence of well marked abnormalities of the blood, lumbar puncture may be necessary to exclude syphilis of the central nervous system, spinal-cord tumors, lesions of the cauda equina and prolapsed intervertebral disk.

BLOOD PICTURE

The blood picture in well developed pernicious anemia is typical of diminished productivity of the bone marrow with decreased numbers of white blood cells and blood platelets, as well as of red blood cells. The red-cell count is usually below 2,500,000. The mean corpuscular volume of the red blood cells is large (110 to 160 cubic microns). Some increase in size is prone to occur before there is any outspoken reduction of the red-cell count. The mean corpuscular hemoglobin concentration is 32 per cent or more, and the color index almost always is above 1. The plasma pigments are usually increased, with an elevation in the indirect van den Bergh reaction.

*From the Medical Service Cushing Veterans Administration Hospital. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and conclusions drawn by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Chief, Medical Service, Cushing Veterans Administration Hospital.

The red cells in the untreated patient may show practically any of the morphologic abnormalities known to occur, except pronounced achromia. A large percentage of deeply stained oval cells, usually macrocytes, is a particular feature. Cells smaller than normal and tiny microcytes are also seen, so that distinctly marked variation in size often occurs. All forms of abnormal shapes may be present, the most bizarre being among the cells of medium and smaller size. Diffuse polychromatophilia and punctate basophilia, are common but reticulocytes above 3 per cent are unusual in the untreated patient. A variety of nucleated red blood cells may rarely be seen, usually in small numbers. With the decreased total number of white cells, the lymphocytes are usually relatively increased. The granulocytes tend to be large, with increased lobulation of the nuclei. Occasionally, the eosinophils are moderately increased. They may reach over 50 per cent after administration of raw liver, but not after cooked liver or liver extract by mouth. The platelets, although generally diminished, rarely fall below 40,000.

The typical blood-cell picture is easily recognized, but when cases are seen early or in remission, changes in the blood may be absent or slight. The finding of a high color index and a distinctly increased mean corpuscular volume, however, does not necessarily indicate pernicious or a related anemia, since types of macrocytic anemia that are unrelated to pernicious anemia occur.

Bone Marrow

In the severely anemic patient with pernicious anemia the active bone marrow is always increased in amount and may extend throughout the long bones. This dark-red marrow shows microscopically great proliferation of primitive red blood cells, often appearing in large sheets obliterating the structural details, so that the white-cell and platelet-forming centers are fewer than normal and the areas occupied by fat cells greatly reduced or absent. As in experimental anemias in animals, the degree of primitive red-cell proliferation appears to be in direct proportion to the severity of the anemia. However, in spite of the continued presence of the stimulus of anoxia due to anemia, normal maturation into erythroblasts and adult erythrocytes does not occur until the antipernicious-anemia principle is supplied. When this is done there is maturation of the primitive cells within a matter of hours through the normoblastic stage and then to reticulocytes and mature erythrocytes within a few days. This occurs prior to any significant increase in the hemoglobin content of the peripheral blood. Within a short time the bone marrow of a patient with pernicious anemia who has been adequately treated with liver extract or vitamin B_{12} returns to an essentially normal state. That the stimulus of anoxia due to anemia is also partly responsible for the great proliferation of the primitive cells has been demonstrated by the work of Davidson and his associates,[1] who reported the reversion of the megaloblastic marrow without liver therapy following the transfusion of sufficient blood completely to relieve the anemia.

Red-Cell Dynamics

It has been known for many years that there is an increased excretion of bile pigments in the urine and stools of patients with pernicious anemia in relapse. This has often been explained as dependent on increased destruction of circulating red blood cells. Indeed, Loutit,[2] employing the Ashby technic, determined that the erythrocytes of 2 patients with untreated pernicious anemia had maximum survival times of twenty-one and sixty days when transfused into normal recipients, in contrast to the normal expected survival of approximately one hundred and twenty days. The absence of an abnormal hemolytic factor in the patient with untreated pernicious anemia has been demonstrated by recent studies[2, 3] showing that normal red blood cells transfused into patients with pernicious anemia survive the normal span.

Dobriner and Rhoads[4] have shown that there is an increased excretion of both coproporphyrin I and urobilin in patients with pernicious anemia in relapse, which returns to normal after liver therapy. Since they believe that coproporphrin I is a by-product of hemoglobin synthesis and not a breakdown product of its destruction as urobilin is, they consider the increased excretion of both pigments to indicate that there is increased production as well as increased destruction of red blood cells during relapse of pernicious anemia.

London et al.[5] have employed N^{15}-labeled glycine in the study of heme synthesis and red-cell dynamics in various disorders. Glycine is specifically utilized for the biologic synthesis of the protoporphyrin of hemoglobin. Hence the administration of labeled glycine results in the production of erythrocytes containing labeled heme, which remains in the cell until the cell disintegrates. Little, if any, of the heme released by cell destruction is reutilized for new hemoglobin synthesis. London and his associates, by thus using labeled glycine, have been able to determine that the rate of red-cell formation in a patient with pernicious anemia in relapse is approximately half the normal rate, and that the mean survival time of the red blood cells is about seventy-two days. It was accordingly apparent that the very large amounts of bile pigment excreted in this disease could not be derived from the destruction of circulating red blood cells. Their studies,[5, 6] to be reported in full later, suggest that a large portion of the bile pigment excreted in the feces is derived from one or more of the following sources: hemoglobin of red blood cells destroyed in the bone marrow or shortly after

reaching the peripheral blood; porphyrin not utilized for hemoglobin production; or direct synthesis of bile pigment via a pathway that does not involve degradation of a porphyrin ring.

Pathogenesis

Castle Theory

Castle's[7] theory of the pathogenesis of pernicious anemia and related macrocytic anemias is now well established. He and his associates demonstrated that the gastric secretion of patients with classic pernicious anemia is deficient in an essential thermolabile constituent ("intrinsic factor"). This material is not rennin, pepsin or gastric lipase[8] but bears close similarity to a proteolytic enzyme found in gastric juice, active at pH 7.4, which may be an alpha-aminopolypeptidase.[9] However, an alpha-aminopolypeptidase prepared from calf thymus by J. S. Fruton failed to exhibit intrinsic factor activity, and normal human gastric juice does not exhibit aminopolypeptidase activity in vitro.[10] Although Meulengracht[11] found the pyloric region of the pig stomach to be most potent in the treatment of pernicious anemia, Fox and Castle[12] demonstrated that in the human stomach greatest activity resides in the fundus (which is the seat of the well known mucosal atrophy in pernicious anemia).

The administration of normal gastric secretion alone is not sufficient to produce a remission in patients with pernicious anemia but must be administered in association with a food factor ("extrinsic factor"), which has been found in such diverse foods as beef muscle, milk, eggs, tomatoes, rice polishings and yeast.

Whether or not the alimentary tract of the patient with pernicious anemia suffers from a degree of impermeability not found in normal man is not altogether clear. However, the flat glucose and vitamin A tolerance curves seen in this disease suggest a diminished capacity for absorption. The fact that liver extract is sixty to a hundred times more effective by injection than by mouth likewise suggests a factor of intestinal impermeability. Studies with vitamin B_{12}, described below, indicate that this differential can be reduced, but not abolished, by the concomitant oral administration of normal human gastric juice. In the classic case of Addisonian pernicious anemia a diminution in the amount of gastric factor decreases the amount of liver principle, which in turn may lead to an impaired appetite with a consequent decrease in the intake of the food factor and possibly increased intestinal impermeability. Castle and his associates[8] have suggested that such an unstable cycle is responsible for the "spontaneous" remissions and relapses frequently observed in patients before the days of liver therapy but never seen in their experience when the diet is completely devoid of extrinsic factor. In sprue, impaired intestinal permeability may be the primary factor, followed by a decreased intake of the food factor as a result of anorexia, leading to the same deficiency of liver principle in the presence of a normal gastric secretion.

Pteroylglutamic Acid (Folic Acid)

In 1945, it was demonstrated that pteroylglutamic acid (a growth factor for many bacteria) was capable of duplicating some of the hematologic effects of liver extract in pernicious and related macrocytic anemias.[13] As little as 1 mg. of free pteroylglutamic acid a day is sufficient to produce a hematopoietic response.[14]

Pteroylglutamic acid occurs in many foods, particularly those of vegetable origin, in the form of conjugates,[15] containing two to six or more additional glutamic acid groups. If the patient with pernicious anemia will respond to 1 mg. of the free acid daily there must then be some defect in his absorption or utilization of these conjugates. Enzymes known as conjugases, capable of splitting the conjugates and releasing the free acid, are present in many animal tissues, in normal persons and in patients with pernicious anemia.[16]

Indeed, Wilkinson and Israëls[17] have shown that two synthetic conjugates (pteroyl-tri-γ-glutamic acid and pteroyl-di-α-glutamic acid) given orally or parenterally to patients with pernicious anemia will produce expected reticulocyte and red-cell responses. It is true that the doses used were large (80 to 140 mg. daily), and that both the conjugates actually employed were synthetic, although the triglutamic acid does occur naturally. However, specific inhibitors of the conjugases exist in many natural sources of pteroylglutamic acid conjugates. Accordingly, Swendseid et al.[18] studied the urinary excretion of pteroylglutamic acid in normal subjects after the administration of free and conjugated forms. They found that the greater the amount of conjugase inhibitor present in the source of the conjugate, the less was the urinary excretion of the free acid. They then found that patients with pernicious anemia in relapse failed to liberate the free acid from preparations of conjugates containing inhibitors.[19] However, patients with pernicious anemia maintained in remission by liver extract were apparently able to liberate pteroylglutamic acid from its conjugates. They also noted that patients with pernicious anemia in relapse excrete less pteroylglutamic acid in the urine than normal subjects do, but after liver therapy this is increased.[19] It has also been observed that in certain cases of sprue the administration of pteroylglutamic acid conjugates together with liver extract is followed by a larger excretion of free acid in the urine than when the conjugates are administered alone.[20]

Further light on the inter-relation of various nutritional factors is afforded by the studies of

Ruegamer et al.,[21, 22] who rendered dogs niacin deficient by means of a suitable diet and the administration of Sulfasuxidine to prevent biosynthesis of the vitamin by micro-organisms in the gastrointestinal tract. They found that the resulting deficiency syndrome, which includes anemia, will respond at first to the administration of niacin. However, the animals will later respond only when either liver extract or pteroylglutamic acid is added, and will exhibit a complete remission only when all three factors are given. Similarly, Heinle and his co-workers[23, 24] have shown that an induced anemia in swine will at first respond to pteroylglutamic acid alone. Later, only a partial response occurs with the same material or with liver extract, but if both are given together recovery occurs.

There is also evidence[25] that pteroylglutamic acid antagonists may inhibit the responses of patients with pernicious anemia to liver extracts, and that liver extract will not prevent the cytologic changes that may be induced in embryonated eggs by these antagonists.[26]

Pteroylglutamic acid and its conjugates, unlike liver extracts potent in pernicious anemia, "extrinsic factor" and animal "protein factor," are found largely in vegetable sources and are less heat stable. Gastric juice does not liberate the free acid from pteroylglutamic acid conjugates, nor does it in any way augment the effectiveness of the free acid or its conjugates.[16] Purified liver extracts will not replace pteroylglutamic acid in the nutritional requirement of certain bacteria and animals.[27]

The introduction of synthetic pteroylglutamic acid in the treatment of pernicious anemia was at first considered a major therapeutic advance that would permit patients to be maintained without the necessity of receiving liver extract by injection. However, before many months went by, it became apparent not only that pteroylglutamic acid failed to protect the nervous system against the progression of subacute combined degeneration of the spinal cord but also, in a number of cases, that fulminating neurologic relapse seemed to be related to its administration.[28] Recently, Israëls and Wilkinson[29] reported that 13 of 17 patients with pernicious anemia, who had no neurologic manifestations at the time treatment with pteroylglutamic acid was begun, developed subacute combined degeneration of the spinal cord requiring liver extract or stomach preparations for relief, and that 3 patients with initially moderate neural involvement became worse under pteroylglutamic acid therapy. Schwartz et al.[30] have observed 31 neurologic relapses over a period of three and a half years of pteroylglutamic acid therapy in 59 patients with pernicious anemia.

Increasing the dose of pteroylglutamic acid does not benefit neural relapse and in fact may even make it worse. A few observations[31] suggest that when large doses of folic acid are administered with liver extract, neurologic relapse may occur that will continue in spite of the administration of liver extract until the folic acid is omitted. This has not been confirmed. It has been suggested that pteroylglutamic acid in patients with pernicious anemia interferes with the normal glutamic acid metabolism of the nervous system just as, for example, the para-aminobenzine sulfonamides may interfere with the normal para-aminobenzoic acid metabolism. However, corroborative evidence for such an action is lacking, and it may well be that a photofission product present in commercial preparations (2-amino-4-hydroxy-6-formyl pteridine) is responsible, since freshly recrystallized pteroylglutamic acid does not significantly inhibit the metabolism of brain-cell suspensions, even when present in high concentrations, as the usual pteroylglutamic acid supplied for clinical use does.[32] The fact that subacute combined degeneration of the spinal cord and neural disturbances following the use of pteroylglutamic acid are virtually nonexistent in patients without achylia gastrica suggests that the latter is a prerequisite for the neural disturbances ascribed to pteroylglutamic acid. Consequently, as might have been anticipated, the daily administration of 20 mg. of pteroylglutamic acid for at least one year to 45 patients without anemia produced no hematologic or neural abnormalities.[33]

Schieve and Rundles[34] have recently shown not only that pteroylglutamic acid is inadequate for the prevention of the spinal-cord lesions but also that the glossitis of pernicious anemia may fail to respond to its administration or may actually develop during its use. In several such cases, prompt healing of the tongue has followed the injection of vitamin B_{12}.

The action of pteroylglutamic acid in pernicious anemia is clearly an incomplete one. The mechanism of action remains obscure. One may speculate that in the absence of the specific antipernicious-anemia factor the patient becomes incapable of fully utilizing natural sources of pteroylglutamic acid and hence develops secondarily a deficiency of pteroylglutamic acid in addition to the primary lack of the antipernicious-anemia factor. Welch and Heinle[23] have suggested that there is characteristically an incomplete deficiency of both factors during relapse and that the removal of either deficiency increases the over-all rate of synthesis of some compound in the formation of which both factors are catalytically involved. Failure of patients to respond to one factor, followed by response to the other, implies that a complete deficiency of the second substance had prevailed.

Vitamin B_{12}

Historical Background

In May, 1947, Shorb[35] announced that *Lactobacillus lactis* (Dorner) failed to grow in an amino

acid basal medium containing all the synthetic components of the vitamin B complex and the "tomato-juice" growth factor unless supplemented with certain preparations of liver extract. Several months later she established the fact that there was a linear relation between the content of the *L. lactis* growth factor of liver extracts and their potency against pernicious anemia.[36] A year later workers[37] at the Merck Research Laboratory succeeded in purifying this factor until they obtained a red crystalline material so potent that 1.3 by 10^5 microgm. per cubic centimeter of culture medium was capable of supporting half maximal growth of *L. lactis* under the conditions of testing. They named the material vitamin B_{12}, noting that it appeared to be one of the most biologically active substances known. Only botulinus toxin and plutonium appear to have comparable activity.

Simultaneously, the late Randolph West[38] reported that crystalline vitamin B_{12} was effective in producing remissions when injected in microgram doses in patients with Addisonian pernicious anemia. Subsequent studies suggested that 1 microgm. of crystalline vitamin B_{12} was equivalent in potency to 1 *U.S.P.* unit of injectable liver extract, although evidence has recently been presented implying that this is an overestimate and that vitamin B_{12} is only half to a third this potent.[39, 40]

Independently and at approximately the same time, E. Lester Smith,[41] of the Glaxo Laboratories in England, employing partition chromatography, isolated from ox liver two red pigments highly active in pernicious anemia as determined by clinical testing.[42] Subsequently, both groups of workers demonstrated the presence of cobalt in their material,[43, 44] thus suggesting for the first time that this trace element might be essential for species other than ruminants. It was quickly shown that cobaltous ion itself was inactive for *L. lactis* and without effect in pernicious anemia.[44] The average daily dietary intake of cobalt by man has been estimated at two thousand times the amount present in 1 microgm. of vitamin B_{12}.

It is of interest that the material in liver effective in pernicious anemia, sought by chemical means and human assay for two decades, was finally isolated independently and almost simultaneously by two groups of workers, one employing *microbiologic assay*, and the other *physical means* and human assay.

Physical and Chemical Properties

Crystalline vitamin B_{12} contains 4.5 per cent cobalt,[42-45] which indicates a minimum molecular weight of 1300, if there is 1-cobalt atom per molecule. This is in agreement with ebullioscopic determinations estimating the molecular weight as 1490 ± 150.[45] By x-ray crystallography, the molecular weight appears to be between 1550 and 1750.[42] It is an optically active, poly-acidic base with absorption maxima at 2780, 3610 and 5500 Å. Analytic data are consistent with the formulas:

$$C_{72}\,H_{98.10}\,N_{14}\,O_{13}\,PCo$$
$$C_{63}\,H_{88.92}\,N_{14}\,O_{13}\,PCo$$

Although Smith[42] originally claimed that each molecule contained 3 atoms of P, Ellis et al.[46] demonstrated that the Co:P ratio was 1:1. On hydrolysis no α-amino acid moiety appears, and hence the vitamin cannot be a polypeptide. There is no evidence for a pterin-type structure. Alkali fusion forms products characteristically reacting like 5-membered nitrogen-containing compounds, including pyrroles, so that a pyrrole or porphyrin-like structure has been suspected.

Lester Smith's[41] original evidence for the existence of a second red factor in liver active in pernicious anemia has been confirmed, and recent evidence suggests that there may be yet a third such factor.[47] An additional factor has been isolated in crystalline form and named vitamin B_{12b}, the designation vitamin B_{12a} having already been applied to an artificially produced hydrogenation product of vitamin B_{12}. Clinical activity appears equal to that of vitamin B_{12}.[48] Absorption spectrums differ slightly. Paper or column-partition chromatography affords a method of obtaining the different factors.[41, 49] Whether the new factors represent chemical modifications of vitamin B_{12} (analogous to the various forms of vitamin D and of penicillin) or whether they are more complex substances incorporating the molecule of vitamin B_{12} (analogous to the conjugates of pteroylglutamic acid with additional molecules of glutamic acid) is as yet unknown.[47]

It is of interest in this connection that certain fermented materials that are quite potent by chick assay exhibit only a fraction of their potency by *Lactobacillus leichmannii* assay,[50] further suggesting the existence of conjugates that are microbiologically incompletely available. Hausmann[51] has reported that concentrates of cow dung or broth cultures of *Streptomyces griseus*, administered intramuscularly to 7 patients with pernicious anemia in amounts that by microchemical cobalt analysis were equivalent to 250 to 1000 microgm. of vitamin B_{12}, were wholly ineffective but that after digestion either with hog-stomach mucosa or with a pancreatic-enzyme extract, the cow-dung factor showed clear hematopoietic activity. He suggests that these materials represent "pre-vitamin B_{12}" or "vitamin B_{12} conjugate" and that under the influence of enzymes that he terms "vitamin B_{12} conjugases" and states are to be found in stomach mucosa, pancreas and kidneys are converted into other forms of vitamin B_{12}.[51] No further data are given.

Microbiologic assay indicates that an aqueous solution of vitamin B_{12} is stable during autoclaving at 121°C. for fifteen minutes, but that it is inac-

tivated at room temperature in 0.015 normal sodium hydroxide solution and in 0.01 normal hydrochloric acid.[44] However, there is evidence that it may be inactivated in culture mediums by autoclaving unless certain protective substances are present.[52]

A few months ago Dr. Karl Folkers[53] announced the chemical nature of one fraction of the vitamin B_{12} molecule to be 5,6-dimethyl benzimidazole. The parent component of this compound, 1,2-diamino-5,6-dimethylbenzene, is a fractional part of riboflavin, a matter of interest in view of the fact that a diet rich in riboflavin appears to favor bacterial synthesis of vitamin B_{12} in the gastrointestinal tract.[54, 55]

Distribution

By assay with *Lactobacillus lactis* (Dorner), Shorb found activity in descending order in refined liver extracts, other liver fractions, brewer's yeast, skimmed milk, peptonized milk and autolyzed yeast[56] and in fairly high amounts in cow manure, fish meal, pancreatin, papain, egg white and egg yolk.[56] She failed to find activity in crude casein, various casein products and digests, yeast nucleic acid, the sodium salt of thymo-nucleic acid and adenylic acid.[56] Little activity was present in an alcoholic extract of whey, soybean-oil meal, gelatin and zein.[56]

Active materials are produced by a variety of micro-organisms, including *Streptomyces aureofaciens* and *S. griseus*,[45, 57] from which source much of the vitamin B_{12} now commercially available is inexpensively obtained.

By rat assay, Lewis et al.[58, 59] have determined that beef kidney contains as much vitamin B_{12} activity as beef liver. Two yeast autolysates were negative, as was 2.0 mg. of thymidine (twenty thousand times the effective dose of crystalline vitamin B_{12}). Two hundred and fifty micrograms each of guanine, adenine, thymine and uracil, in addition to 500 microgm. each of rutin and hesperidin, gave no rat growth.

The same workers found that beef and horse meat were quite active, whereas pork was extremely variable, some samples containing practically no vitamin B_{12} activity, and even the best samples contained less activity than beef. They also found that sheep rumen was active. It is of interest in this connection that when radioactive cobalt (Co^{58}) is fed to sheep, more than half the amount recovered in the feces is in organically bound form and is associated with a high vitamin B_{12} activity.[60]

It is of additional interest that there is a marked diminution in the number of rumen bacteria and alteration of types in cobalt-deficient sheep.[61] Cobalt in 1-mg. daily doses, which will relieve the anemia and anorexia when given by mouth, is inert when administered by injection in the same amount. Vitamin B_{12}, given orally or by injection in amounts comparable to those beneficial in pernicious anemia, is also inert.[62] Thus the cobalt-deficiency syndrome in ruminants appears to be something more than a deficiency of vitamin B_{12}. However, the above data suggest that the bovine and sheep rumen (and possibly the equine cecum) may be the site of vitamin B_{12} formation through bacterial action in the presence of dietary traces of cobalt. The hog has no structure comparable to the rumen or the equine cecum.

In rats depleted of vitamin B_{12} for six weeks, 0.04 microgm. of vitamin B_{12} per gram of kidney was found, and none in liver, heart, small intestine or muscle.[63] When the basal diet was supplemented with vitamin B_{12}, the kidney was found to contain the highest concentration, 0.17 microgm. per gram, with the liver next, 0.08 microgm. followed by the heart, 0.07 microgm., and the small intestine, 0.04 microgm. Only a trace of the vitamin was found in muscle, and the amount in spleen was not measurable.

Relation to Animal-Protein Factor Necessary for Chick Growth

In the year following the announcement that a liver diet cured pernicious anemia, it was noted that hens' eggs did not hatch in normal numbers unless the hens' diet contained some animal protein.[64] Years later, it was observed that proper growth of chicks does not occur when the diet is solely of vegetable origin. The unidentified growth factor or factors are well supplied by many animal proteins and are found in large amounts in fish meal,[65] fish solubles,[66] dried cow manure,[67] whole-liver powders[67] and hens' feces.[68] The last source exhibits increased potency after incubation,[68] suggesting that bacterial action is involved in the formation of the growth factor. There is evidence that the above sources are also good sources of the factor or factors without which the hatchability of hens' eggs is low.[69]

In July, 1948, Ott, Rickes and Wood[70] showed that the animal-protein factor for chick growth could be replaced by the addition of 30 microgm. of vitamin B_{12} to each 1000 gm. of diet, suggesting that vitamin B_{12} was the animal-protein factor for chicks. Although Nichol et al.[71] corroborated this observation in January, 1949, they subsequently[72] found no correlation between the *U.S.P.* potency of liver extracts and their ability to promote chick growth, some highly potent extracts against pernicious anemia exhibiting no chick-growth activity. Subsequently, it has been shown that other materials than vitamin B_{12} are included in the animal-protein factor for chicks and that maximal growth will not occur with vitamin B_{12} alone.[73] Neither liver extract nor vitamin B_{12} alone is effective in correcting an anemia produced in chicks by a diet deficient in folic acid in combination with phenylhydrazine, but folic acid is partially effective;

folic acid and either liver extract or vitamin B_{12} is very effective.[74]

Further data concerning interrelations between various growth factors have been reported.[75] On a semipurified diet, with or without folic acid, vitamin B_{12} or vitamin C stimulates chick growth, and the two together are more effective than either alone. Each vitamin alone stimulates the synthesis of folic acid in vivo as measured by the liver content, and the two together lead to greater liver storage than either alone. It has been suggested that both vitamins have their effect through altering oxidation-reduction potentials in the gastrointestinal tract.

In assessing dietary growth factors for the chick it must be borne in mind that the hens' diets must be controlled, since the adequacy or deficiency of the latter will affect the chick's requirements for growth factors.[76] That vitamin B_{12} is indeed an essential hatchability factor is suggested by the recent observation that the injection of the crystalline vitamin into the albumen of eggs laid by hens on deficient diets leads to significantly greater numbers that hatched, and that growth and feathering of the chicks was superior even to that of chicks supplemented with vitamin B_{12} after hatching.[77]

It should also be noted that a single injection at the beginning of the assay periods meets the chick's needs for a fortnight,[78] indicating a degree of storage or conservation of the vitamin.

(To be concluded)

References

1. Davidson, C. S., Murphy, J. C., Watson, R. J., and Castle, W. B. Comparison of effects of massive blood transfusions and of liver extract in pernicious anemia. *J. Clin. Investigation* **25**:858-869, 1946.
2. Callender, S. T., Loutit, J. F., and Jope, E. M. Discussion on life and death of red blood corpuscle. *Proc. Roy. Soc. Med.* **39**:755-762, 1946.
3. Brown, G. M., Hayward, O. C., Powell, E. O., and Witts, L. J. Destruction of transfused erythrocytes in anaemia. *J. Path. & Bact.* **56**:81-94, 1944.
4. Dobriner, K., and Rhoads, C. P. Metabolism of blood pigments in pernicious anemia. *J. Clin. Investigation* **17**:95-103, 1938.
5. London, I. M., Shemin, D., West, R., and Rittenberg, D. Heme synthesis and red blood cell dynamics in normal humans and in subjects with polycythemia vera, sickle-cell anemia, and pernicious anemia. *J. Biol. Chem.* **179**:463-484, 1949.
6. London, I. M., West, R., Shemin, D., and Rittenberg, D. On origin of stercobilin in humans. *Federation Proc.* **7**:169, 1948.
7. Castle, W. B. Observations on etiologic relationship of achylia gastrica to pernicious anemia. I. Effect of administration to patients with pernicious anemia of contents of normal human stomach recovered after ingestion of beef muscle. *Am. J. M. Sc.* **178**: 748-764, 1929.
8. Castle, W. B., Heath, C. W., and Strauss, M. B. Observations on etiologic relationship of achylia gastrica to pernicious anemia. IV. Biologic assay of gastric secretion of patients with pernicious anemia having free hydrochloric acid and that of patients without anemia or with hypochromic anemia having no free hydrochloric acid, and of rôle of intestinal impermeability to hematopoietic substances in pernicious anemia. *Am. J. M. Sc.* **182**:741-764, 1931.
9. Agren, G., and Waldenström, J. Intrinsic factor activity of highly purified preparations of aminopolypeptidase. *Acta med. Scandinav.* (Supp. 196) **128**:432-455, 1947.
10. Castle, W. B. Personal communication.
11. Meulengracht, E. Presence of antianaemic factor in preparations of dried stomach substance from the cardia, fundus and pylorus respectively. (Preliminary communication.) *Acta med. Scandinav.* **82**:352-374, 1934.
12. Fox, H. J., and Castle, W. B. Observations on etiologic relationship of achylia gastrica to pernicious anemia. IX. Difference in site of secretion of intrinsic factor in hog and in human stomach. *Am. J. M. Sc.* **203**:18-28, 1942.
13. Spies, T. D., Vilter, C. F., Koch, M. B., and Caldwell, M. H. Observations on anti-anemic properties of synthetic folic acid. *South. M. J.* **38**:707-709, 1945.
14. Davidson, S. Folic acid and its conjugates in pathogenesis of megaloblastic anaemia. *Lancet* **2**:814, 1949.
15. Bird, O. D., Bressler, B., Brown, R. A., Campbell, C. J., and Emmett, A. D. Microbiological assay of vitamin Bc conjugate. *J. Biol. Chem.* **189**:631-636, 1945.
16. Heinle, R. W. Folic acid in treatment of macrocytic anemias. *Veterans Admin. Tech. Bull.* (T. B. 10-22), 1946.
17. Wilkinson, J. F., and Israëls, M. C. G. Pteroyl-polyglutamic acids in treatment of pernicious anaemia. *Lancet* **2**:689-691, 1949.
18. Swendseid, M. E., Bird, O. D., Brown, R. A., and Bethell, F. H. Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. II. Urinary excretion studies on normal persons. Effect of conjugase inhibitor. *J. Lab. & Clin. Med.* **33**:23-27, 1947.
19. Bethell, F. H., et al. Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. I. Hematologic and urinary excretion studies on patients with macrocytic anemia. *J. Lab. & Clin. Med.* **32**:3-22, 1947.
20. Suarez, R. M., Welch, A. D., Heinle, R. W., Suarez, R. M., Jr., and Nelson, E. M. Effectiveness of conjugated forms of folic acid in treatment of tropical sprue. *J. Lab. & Clin. Med.* **31**: 1294-1304, 1946.
21. Ruegamer, W. R., Torbet, N., and Elvehjem, C. A. Hematological and growth responses in dogs given liver extracts containing antipernicious anemia factor. *Federation Proc.* **6**:287, 1947.
22. Ruegamer, W. R., Brickson, W. L., Torbet, N. J., and Elvehjem, C. A. Response of dogs to liver extracts containing pernicious anemia factor. *J. Nutrition* **36**:425-435, 1948.
23. Welch, A. D., and Heinle, R. W. Pteroylglutamic acid and antagonists: biological studies. Paper presented at Conference on Preservation of the Formed Elements and of the Proteins of the Blood, Boston, January 6-8, 1949.
24. Heinle, R. W., Welch, A. D., and Shorr, H. L. Interrelation of pteroylglutamic acid and vitamin B_{12} in induced anemia of swine. *J. Lab. & Clin. Med.* **34**:1763, 1949.
25. Meyer, L. M., et al. Studies in pernicious anemia patients treated with liver extract and folic acid antagonists. *Am. J. M. Sc.* **218**:197-203, 1949.
26. Wagley, P. F., and Morgan, H. R. Observations on effects of folic acid antagonists, folic acid, liver extract and vitamin B_{12} on embryonated eggs: preliminary report. *Bull. Johns Hopkins Hosp.* **83**:275-278, 1948.
27. Welch, A. D., Heinle, R. W., Nelson, E. M., and Nelson, H. V. Role of conjugated and free forms of folic acid in control of pernicious anemia. II. Biochemical aspects. *Ann. New York Acad. Sc.* **48**:347-349, 1946.
28. Heinle, R. W., and Welch, A. D. Folic acid in pernicious anemia: failure to prevent relapse. *J. A. M. A.* **133**:739-741, 1947.
29. Israëls, M. C. G., and Wilkinson, J. F. Risk of neurological complications in pernicious anaemia treated with folic acid. *Brit. M. J.* **2**:1072-1075, 1949.
30. Schwartz, S. O., Kaplan, S. R., and Armstrong, B. Long-term evaluation of therapy of pernicious anemia with folic acid. *J. Lab. & Clin. Med.* **34**:1747, 1949.
31. Ross, J. F., Belding, H., and Paegel, B. L. Development and progression of subacute combined degeneration of spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood* **3**:68-90, 1948.
32. Cobb, S., Pearson, O. H., and Hastings, A. B. Inhibitory effects of pteroyl glutamic acid preparations. *Proc. Soc. Exper. Biol. & Med.* **70**:595-597, 1949.
33. Poliakoff, H., Sternbach, A., Walker, W. H., Kascht, R. L., and Meyer, L. M. Administration of folic acid to patients without anemia. *Proc. Soc. Exper. Biol. & Med.* **73**:392, 1949.
34. Schieve, J. F., and Rundles, R. W. Response of liagual manifestations of pernicious anemia to pteroylglutamic acid and vitamin B_{12}. *J. Lab. & Clin. Med.* **34**:439-447, 1949.
35. Shorb, M. S. Unidentified essential growth factors for *Lactobacillus lactis* found in refined liver extracts and in certain natural materials. *J. Bact.* **53**:669, 1947.
36. *Idem.* Unidentified growth factors for *Lactobacillus lactis* in refined liver extracts. *J. Biol. Chem.* **169**:455, 1947.
37. Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. Crystalline vitamin B_{12}. *Science* **107**:396, 1948.
38. West, R. Activity of vitamin B_{12} in Addisonian pernicious anemia. *Science* **107**:398, 1948.
39. Jones, E., Darby, W. J., and Totter, J. R. Pernicious anemia and related anemias treated with vitamin B_{12}. *Blood* **4**:827-844, 1949.
40. Heinle, R. W. Personal communication.
41. Smith, E. L. Purification of anti-pernicious anaemia factors from liver. *Nature, London* **161**:638, 1948.
42. Ungley, C. C. Discussion of macrocytic anaemias; proceedings of Section of Medicine, British Medical Association. *Brit. M. J.* **2**: 154, 1948.
43. Smith, E. L. Presence of cobalt in anti-pernicious anaemia factor. *Nature, London* **162**:144, 1948.
44. Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. Vitamin B_{12}, cobalt complex. *Science* **108**:134, 1948.
45. Brink, N. G., et al. Vitamin B_{12}. IV. Further characterization of vitamin B_{12}. *J. Am. Chem. Soc.* **71**:1854-1856, 1949.
46. Ellis, B., Petrow, V., and Snook, G. F. Chemistry of antipernicious anaemia factors. I. Liberation of phosphorus as phosphate from vitamin B_{12} by acid hydrolysis. *J. Pharm. & Pharmacol.* **1**:287-291, 1949.
47. Smith, E. L. Crystalline anti-pernicious-anaemia factor. *Brit. M. J.* **2**:1367-1369, 1949

48. Lichtman, H., et al. Vitamin B_{12}: some properties and its therapeutic use. *Proc. Soc. Exper. Biol. & Med.* **72**:643-645, 1949.
49. Winsten, W. A., and Eigen, E. Paper chromatography of vitamin B_{12} and related bacterial growth factors. *J. Biol. Chem.* **181**: 109-120, 1949.
50. Hoffmann, C. E., Stokstad, E. L. R., Hutchings, B. L., Dornbush, A. C., and Jukes, T. H. Microbiological assay of vitamin B_{12} with *Lactobacillus leichmannii*. *J. Biol. Chem.* **181**:635-644, 1949.
51. Hausmann, K. Liver extracts, vitamin B_{12}, and thymidine. *Lancet* **2**:962, 1949.
52. Stokstad, E. L. R., et al. Microbiological assay of vitamin B_{12} by *Lactobacillus leichmannii*. *Federation Proc.* **8**:257, 1949.
53. Staff Report. Folkers reports B_{12} progress as Harrison Howe lecturer. *Chem. Eng. News* **27**:3487, 1949.
54. Hartman, A. M., Dryden, L. P., and Cary, C. A. Bacterial synthesis in rat of unidentified growth-promoting factor. *Federation Proc.* **8**:205, 1949.
55. *Idem.* Role and sources of vitamin B_{12}. *J. Am. Dietet. A.* **25**:929-933, 1949.
56. Shorb, M. S. Activity of vitamin B_{12} for growth of *Lactobacillus lactis*. *Science* **107**:397, 1948.
57. Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. Comparative data on vitamin B_{12} from liver and from new source, *Streptomyces griseus*. *Science* **108**:634, 1948.
58. Lewis, U. J., Register, U. D., Thompson, H. T., and Elvehjem, C. A. Distribution of vitamin B_{12} in natural materials. *Proc. Soc. Exper. Biol. & Med.* **72**:479-482, 1949.
59. Register, U. D., Lewis, U. J., Thompson, H. T., and Elvehjem, C. A. Variations in vitamin B_{12} content of selected samples of pork and beef muscle. *Proc. Soc. Exper. Biol. & Med.* **70**:167, 1949.
60. Abelson, P. H., and Darby, H. H. Synthesis of vitamin B_{12} in digestive system of sheep. *Science* **110**:566, 1949.
61. Gall, L. S., Smith, S. E., Becker, D. E., Stark, C. N., and Loosli, J. K. Rumen bacteria in cobalt-deficient sheep. *Science* **109**: 468, 1949.
62. Becker, D. E., Smith, S. E., and Loosli, J. K. Vitamin B_{12} and cobalt deficiency in sheep. *Science* **110**:71, 1949.
63. Lewis, U. J., Register, U. D., and Elvehjem, C. A. Vitamin B_{12} content of various organs and tissues of rat. *Proc. Soc. Exper. Biol. & Med.* **71**:509-511, 1949.
64. Parkhurst, R. T. Vitamin feeds for laying hens. *Univ. Idaho Agr. Exper. Sta. Bull.* **169**:38, 1927.
65. Combs, G. F., Heuser, G. F., and Norris, L. C. Further evidence for unidentified chick growth factor. *Poultry Sc.* **27**:238-240, 1948.
66. Robblee, A. R., Nichol, C. A., Cravens, W. W., Elvehjem, C. A., and Halpin, J. G. Effect of hen diet and chick diet on need of chicks for unidentified growth factor. *Poultry Sc.* **27**:422-447, 1948.
67. Nichol, C. A., Robblee, A. R., Cravens, W. W., and Elvehjem, C. A. Distribution of unidentified chick growth factor. *Poultry Sc.* **27**:438-441, 1948.
68. Kennard, D. C., Bethke, R. M., and Chamberlin, V. D. Built-up floor litter source of dietary factors essential for hatchability of chicken eggs. *Poultry Sc.* **27**:477-481, 1948.
69. Cravens, W. W., and Halpin, J. G. Effect of pteroylglutamic acid and unidentified factor on egg production and hatchability. *J. Nutrition* **37**:127-138, 1949.
70. Ott, W. H., Rickes, E. L., and Wood, T. R. Activity of crystalline vitamin B_{12} for chick growth. *J. Biol. Chem.* **176**:1047, 1948.
71. Nichol, C. A., Dietrich, L. S., Cravens, W. W., and Elvehjem, C. A. Activity of vitamin B_{12} in growth of chicks. *Proc. Soc. Exper. Biol. & Med.* **70**:40-42, 1949.
72. Nichol, C. A., Robblee, A. R., Cravens, W. W., and Elvehjem, C. A. Growth response of chicks to antipernicious anemia preparation. *J. Biol. Chem.* **177**:631-639, 1949.
73. Stokstad, E. L. R., Jukes, T. H., Pierce, J., Page, A. C., Jr., and Franklin, A. L. Multiple nature of animal protein factor. *J. Biol. Chem.* **180**:647-654, 1949.
74. Nichol, C. A., Harper, A. E., and Elvehjem, C. A. Effect of folic acid, liver extract, and vitamin B_{12} on hemoglobin regeneration in chicks. *Proc. Soc. Exper. Biol. & Med.* **71**:34-37, 1949.
75. Dietrich, L. S., Nichol, C. A., Monson, W. J., and Elvehjem, C. A. Observations on interrelation of vitamin B_{12}, folic acid, and vitamin C in chick. *J. Biol. Chem.* **181**:915-920, 1949.
76. Wiese, A. C., Petersen, C. F., and Lampman, C. E. Variability of protein supplements in hen's diet in supplying unidentified factor or factors essential for chick growth. *Poultry Sc.* **27**:466-470, 1948.
77. Lillie, R. J., Olsen, M. W., and Bird, H. R. Role of vitamin B_{12} in reproduction of poultry. *Proc. Soc. Exper. Biol. & Med.* **72**:598-602, 1949.
78. Lillie, R. J., Denton, C. A., and Bird, H. R. Relation of vitamin B_{12} to growth factor present in cow manure. *J. Biol. Chem.* **176**: 1477, 1948.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 36311

PRESENTATION OF CASE

A fifty-three-year-old woman was admitted to the hospital because of abdominal pain.

Five days before entry there was the sudden onset of severe pain in the right upper quadrant of the abdomen that radiated through to the mid-back. This was associated with several bouts of vomiting during the first two days of the illness, but then vomiting ceased although the pain persisted. She was very thirsty and took only fluids by mouth. Three days before admission she became dyspneic. A physician saw her at this time and found a low blood pressure, a regular heart rhythm and a tender mass in the right upper quadrant. He gave her no medication except glucose by mouth. Two days before entry she began to have ankle swelling, and during the following two nights she had paroxysmal dyspnea. She had no fever or chills. On the day of admission her physician found sugar in the urine.

The patient had diphtheria at the age of twenty, and six years later was admitted to a state hospital for three months because of a "nervous breakdown." There had been no previous operations or injuries. There was no history of heart disease, hypertension, jaundice or previous abdominal pain. She had occasional constipation for which she took Epsom salts and had had nocturia (one time) for an unknown period.

Physical examination revealed an obese, swarthy, dyspneic woman who appeared older than her given age. The neck veins were distended. There were moist rales, diminished breath sounds and dullness at both bases. The heart size was hard to determine, but it seemed somewhat enlarged. There was normal sinus rhythm, with a faint protodiastolic gallop at the left lower sternal border. The pulmonic second sound was greater than the aortic, and there were no rubs or murmurs. The abdomen was obese and protuberant. The liver edge was palpable three fingerbreadths below the costal

margin and was very tender. There was no rebound tenderness, and the spleen and kidneys were not palpable. There was a small, easily reducible umbilical hernia. Peristalsis was quiet. There was ++ edema of the lower legs. The left leg was pale, and on the left foot there was a vesicle. The dorsalis-pedis and posterior-tibial pulsations were absent, but the femoral pulses were present.

The temperature was 98.6°F., the pulse 100, and the respirations 25. The blood pressure was 145 systolic, 85 diastolic.

The urine had a specific gravity of 1.018 and gave a +++ test for albumin, and the sediment contained an occasional white blood cell. A urine test for sugar was red but negative for acetone. Examination of the blood showed a hemoglobin of 15.0 gm. and a white-cell count of 16,000, with 88 per cent neutrophils. An electrocardiogram was interpreted as follows: normal rhythm at a rate of 90, PR interval of 0.16 and QRS complex of 0.08 second, normal axis, slight inversion of the T waves in Leads 1, AVL and V_4, V_5 and V_6; upright T waves in Leads 2, 3, AVF and V_1, V_2 and V_3; and flat T waves in Lead AVR. A roentgenogram of the chest showed a rather large quantity of fluid in the left pleural space and a questionable amount in the right. There was a hazy ground-glass density in both lung fields that appeared more pronounced centrally. There was also a mottled hazy density in the right-lower-lung field near the diaphragm. The heart shadow could not be adequately seen. A plain film of the abdomen showed a large gallstone superimposed on the right eleventh rib and lying somewhat more medially than usual. The liver could not be adequately evaluated. The spleen was not enlarged, and no unusual loops of gas-filled bowel were recognized.

On the second hospital day the patient seemed somewhat more at ease and no longer complained of pain. A fasting blood sugar was 236 mg., the nonprotein nitrogen 31 mg., and the total protein 5.2 gm. per 100 cc.; the carbon dioxide was 32.9 milliequiv. per liter. The serum van den Bergh was 0.3 mg. per 100 cc. direct and 0.5 mg. per 100 cc. total; the prothrombin time was 22 seconds (normal, 17 seconds), or 65 per cent, and the serum amylase 15 units per 100 cc. A blood Hinton test was negative. A repeat electrocardiogram showed no significant changes and a second roentgenogram of the chest showed in addition to fluid a somewhat enlarged heart. The temperature rose to 99°F., and the white-cell count to 22,800. The patient was treated with insulin, digitoxin, Mercuhydrin, heparin, Dicumarol and antibiotics, but despite this therapy showed only slight clinical improvement. A thoracentesis on the fourth hospital day produced 1000 cc. of light-orange fluid containing 2400 red cells and 80 white cells per cubic millimeter. Some improvement in color was noted in the legs after the patient was placed on intermittent venous occlusion. After nine days the urine had cleared of sugar. The white-cell count, however, remained at levels ranging from 15,000 to 22,000, and the temperature ran an irregular course with elevations to 100°F. Following the introduction of anticoagulant therapy, the prothrombin time was maintained between (less than) 10 and 45 per cent. On the eleventh hospital day the patient complained of abdominal pain and became restless and slightly cyanotic. Several hours later, while being turned in bed, she suddenly died.

Differential Diagnosis

Dr. Daniel S. Ellis*: The problem to me is why did this patient have abdominal pain and why did she die? One is given the information that she had a gallstone and that frequently is a cause of pain with radiation to the mid-back from the right upper quadrant. The patient's pain as described was perfectly characteristic of pain due to biliary colic. It is a little unusual that she had no fever, no chills, no history of jaundice and no previous history of indigestion. One wonders whether or not she had an acute pancreatitis. She was thought to have a mass in the right upper quadrant by the physician who examined her originally. Later she had a palpable liver that was tender, and no mention was made of a mass. We are not told of any pain extending to the left of the mid-line or radiating to the back on the left side. We are not told of any tenderness over the body of the pancreas other than that which was attributed to a palpable liver. There was no elevation of the serum amylase. As a matter of fact it was 15 units per 100 cc., which is perfectly normal.

There seems to be no question that when this patient came into the hospital she soon developed congestive heart failure. The etiology of the heart disease is not indicated in the record anywhere unless the clue that she had peripheral vascular disease indicates that she had generalized arteriosclerosis and chronic myocardial insufficiency on the basis of coronary-artery disease, which I think she did have. One wonders whether or not she had a coronary occlusion with queer distribution of pain, which was referred to the right upper quadrant with radiation to the back. The electrocardiogram as I interpret it showed myocardial weakness, possibly left ventricular weakness and possibly some electrolyte imbalance. However, the last is not borne out in the reports of the blood chemical findings. I cannot get any clue from the electrocardiogram that this patient had an acute myocardial infarction, and unless the cardiologist will help me out, I will assume that the record represents a myocardial weakness and nothing more. Another cause for pain in this region might be pulmonary infarction, and the patient might well have had pulmonary emboli, the legs being the probable

*Assistant physician, Massachusetts General Hospital.

source. The exact nature of the peripheral vascular disease is not clear, but inasmuch as the physicians ordered intermittent venous occlusion I will assume that she had some form of arterial insufficiency. Possibly, the intermittent venous occlusion stirred up some thrombi from the veins.

Dr. Wyman, you looked at the films with me earlier. Would you like to say something about them now?

DR. STANLEY M. WYMAN: These three sets of films taken within a three-day interval are poor films on a very sick, very obese woman. The fluid in the left pleural space is well seen on all three examinations. There is some fluid in the right pleural space, I suppose. There is linear density adjacent to the minor fissure on the right, and there is some density in the right-lower-lung field about the diaphragm. The heart shadow is probably enlarged in the region of the right ventricle. There may be a little calcification in the aortic arch, but I am not certain of that. As Dr. Ellis says, it is impossible to exclude sizable infarcts in the lungs. The plain film of the abdomen shows a gallstone.

DR. ELLIS: Do you think that gallstone is out of place as the protocol leads me to believe?

DR. WYMAN: I believe the duodenal cap lies adjacent to it. I think it could be out of place in that it might lie toward the neck of the cystic duct. I do not believe it is outside the gall bladder.

DR. ELLIS: I wonder whether the mass felt before admission was the tender liver or whether it was definitely thought to be something else. I assume that the left side of the chest was the one that was aspirated, Dr. Mallory.

DR. TRACY B. MALLORY: Yes, it was.

DR. ELLIS: The other condition that would cause continued pain in the right upper quadrant radiating through to the back might be a large gallstone eroding through the gall bladder into the duodenum or elsewhere into the abdominal cavity. There were no clues that she had air in the biliary tree, which is a frequent accompaniment of such a phenomenon. She had an elevation of the white-cell count but no evidence from the physical examination of a generalized peritonitis. Perhaps whoever saw the patient could tell us whether or not she had any abdominal rigidity.

DR. MALLORY: I believe she did not have abdominal rigidity.

DR. ELLIS: I have considered the following conditions as causes of pain: acute cholecystitis with cholelithiasis; a gallstone perforating into the peritoneal cavity; pancreatitis, for which we have no supportive evidence on physical examination or by laboratory tests; a possible coronary occlusion with queer distribution of pain; and multiple pulmonary infarcts. The only other thing that I think could explain this patient's pain is a chronically congested, tender liver. That to me makes more sense considering the rest of the picture. We know that she had congestive heart failure and peripheral edema. The liver was palpable and tender, and I think if it was congested as the lungs were that she might very well have had severe pain radiating to the back on that basis alone.

That brings me to the cause of death. The death was sudden, like that seen in a vascular phenomenon of some kind, such as an embolus, most likely pulmonary or into the right heart, or possibly mesenteric but I do not see why the latter should cause cyanosis. Again she may have died of an acute coronary insult, but I cannot do any more than surmise about that possibility. There did not seem to be any evidence that the heart or a major vessel was perforated. There was no mention that the patient was in shock. The record stated definitely that she was cyanotic. I will have to discard perforation of a major vessel.

Before concluding I should like to know something about the nature of the vesicle on the foot. Was that of the type seen in peripheral vascular disease with early necrosis and gangrene?

DR. MALLORY: I think it was except that it cleared up, which was a little remarkable under the circumstances.

DR. ELLIS: The patient's white-cell count bothers me a bit. I would like to think that that was on the basis of something going on in the gall bladder, in the right upper quadrant or in the pancreas. On the other hand she had relatively little fever. The white-cell count could be explained on the basis of a vascular phenomenon such as multiple infarcts.

I have come to the conclusion that this patient's primary disease was heart failure due to coronary-artery disease, myocardial insufficiency and a large, swollen, congested liver. The most likely cause of the pain seems to be the liver. We know that she had cholelithiasis, and she must have had some chronic cholecystitis. I am prepared to be told that this gallstone might have been giving her trouble, but I will put that as my second guess. I think that the cause of death was a massive pulmonary embolism. The diabetes was not very severe. People can have severe pain with diabetic acidosis but whatever acidosis she had was of mild degree, and I do not believe the diabetes played any part in the picture. I shall stick to a primary diagnosis of coronary-artery disease, congestive heart failure, congested liver, multiple pulmonary infarcts, generalized arteriosclerosis, cholelithiasis and chronic cholecystitis.

A PHYSICIAN: Dr. Ellis, what do you think precipitated the heart failure? Do you think it was secondary to cardiac infarction?

DR. ELLIS: I should think it might have been secondary to pulmonary emboli or a chronic myocarditis. I do not know why she had heart failure. Apparently, that was not in the picture until after the abdominal pain occurred. That is hard for me

to explain really. If she had infection or something going on in the abdomen below the diaphragm with a weak heart that might have precipitated the heart failure. I cannot exclude an acute myocardial infarction.

DR. SAMUEL MCD. MCCANN: She certainly was not sick very long, but I think we have to consider the possibility of something on the valves that might have precipitated multiple peripheral embolization.

DR. MALLORY: She was seen repeatedly by surgical consultants. I am sorry they are not here to discuss the case. The first two or three days that she was in the hospital, the possibility of acute cholecystitis was very seriously considered. Eventually, the surgeons decided that was relatively unlikely. Also, they were distressed for a period about the circulation of the legs, but under the intermittent pressure treatment that cleared up; all the discoloration of the legs had disappeared entirely by the time of autopsy, and there was no suggestion of gangrene although at one time it had seemed incipient.

CLINICAL DIAGNOSES

Diabetes mellitus.
Coronary-artery disease.
? Myocardial infarction.
? Cholecystitis.
? Biliary colic.
Femoral-artery thrombosis, bilateral.

DR. ELLIS'S DIAGNOSES

Coronary-artery disease.
Congestive heart failure.
Congested liver.
Multiple pulmonary infarcts.
Generalized arteriosclerosis.
Cholelithiasis.
Cholecystitis.

ANATOMICAL DIAGNOSES

Coronary sclerosis, severe.
Myocardial infarcts, recent.
Acute fibrinous pericarditis.
Multiple pulmonary emboli.
Congestion of liver, marked.
Cholelithiasis.
(Diabetes mellitus.)
Intercapillary glomerulosclerosis, slight.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed very severe coronary sclerosis as the primary disease. There were two areas of infarction in the myocardium, one at the apex of the left ventricle, which was overlain by a partially organized thrombus and had the appearance of being of perhaps ten days' to two weeks' duration. There was a second and much fresher infarct along the lateral margin or base of the left ventricle, extending almost up to the valve ring, probably of less than three days' duration. The coronary arteries were reduced to pin-point diameter, but no points of total occlusion could be found. There was everywhere a minute lumen on section. There were also multiple pulmonary emboli, one large one in the artery leading to the left lower lobe, which showed hemorrhagic discoloration and an early stage of infarction. There were multiple emboli occluding all branches to the various lobes of the right lung, but there was no infarction on the right. The liver was markedly congested. The gall bladder contained a single stone, which was of considerable size and could not possibly have passed into the cystic duct. There was no active cholecystitis whatever, and I think that Dr. Ellis's explanation of the pain was probably correct. It seems unlikely that the gallstone was responsible. Another factor that might have caused this pain was the presence of a fairly acute, fibrinous pericarditis, which one often sees with myocardial infarction. I do not know whether pain from pericarditis ever radiates to the back as this pain did. The kidney showed very marked vascular disease and traces of intercapillary glomerular sclerosis in some of the glomeruli, which would go with the mild diabetes, but I do not believe it was an important part of the picture. There was a small infarct in the spleen.

DR. BENJAMIN CASTLEMAN: I should like to ask Dr. Ellis whether he thinks the cardiac infarction could have produced that type of abdominal pain.

DR. ELLIS: I am sure it could have, but I do not think it did in this case. With the liver in the state that it was I would much rather say that was the cause of the pain. The original severe attack of pain seems much more likely to have been associated with the coronary-artery disease than the steady, dull aching pain in the abdomen that she complained of constantly. I am a little bit surprised that the electrocardiogram did not show more, or perhaps I did not interpret it correctly.

CASE 36312

PRESENTATION OF CASE

A sixty-two-year-old man was admitted to the hospital because of intermittent vomiting.

Four months before entry the patient noted the onset of belching and crampy para-umbilical pain about four hours after a large meal. The pain was slightly more marked on the left than on the right. A short time later he vomited a large amount of yellowish material containing some partially digested food. During the next month and a half he had several similar but less severe attacks, and therefore he consulted his physician. A gastrointestinal series and a Graham test were said to be negative. Since that time at intervals of about

eight to ten days he had had attacks usually lasting about three hours and occurring after large evening meals. These attacks were characterized by midabdominal pain, belching and generalized bloating followed by vomiting. The pain occasionally went through to the right side of the back, and symptoms were always relieved by vomiting. At times food taken two or three meals before the attack could be recognized in the vomitus. During the ten days just before admission, attacks had been more frequent, and he had a sensation of gradual "filling up" over a two-day period, followed by abdominal pain and vomiting. The pain was never severe enough to cause him to double up, and there had been no hematemesis or melena although the stools decreased and were somewhat lighter. There had been no fever, chills or jaundice. Although he had lost 10 pounds in weight during the four-month period he had continued to feel well and worked every day. He had been taking tincture of belladonna for two and a half months before entry.

The past history and review of the systems were noncontributory.

Physical examination showed a well developed man who appeared chronically ill but was in no acute distress. The skin and mucous membranes were slightly dry, and the tongue was coated. There were a few small palpable axillary lymph nodes bilaterally. The heart sounds could not be well heard, and the heart seemed to be displaced or obscured by a large, dilated stomach. There was slight abdominal distention with what seemed to be a large dilated stomach in the left upper quadrant. This area was tympanitic, whereas the rest of the abdomen was relatively dull. There was a suggestion of a cylindrical mass at the left rectus border in the upper abdomen. There was very slight tenderness in the left lower quadrant. Bowel sounds were depressed, and only occasional tinkles were heard.

The temperature was 100.4°F., the pulse 78, and the respirations 20. The blood pressure was normal.

A urine specimen was normal. Examination of the blood revealed a hemoglobin of 13.8 gm., and a white-cell count of 6700. The blood sodium was 142.0 milliequiv., and the potassium 4.7 milliequiv. per liter, the protein 5.9 gm., and the nonprotein nitrogen 25 mg. per 100 cc., and the prothrombin time 20 seconds (normal, 17 seconds). The sedimentation rate was 0.4 mm. per minute. A gastrointestinal series showed a normal esophagus. The stomach, the duodenum and the jejunum up to a point about 2 feet from the ligament of Treitz were grossly dilated with fluid (Fig. 1). In this region the lumen of the bowel was narrowed. The bowel distal to the area, which could only be seen by virtue of small amounts of barium, was of normal caliber. No tumor edge could be made out in the obstructed area, but the examination was considered not entirely satisfactory. Anteroposterior films made with the patient in the supine and in the erect positions showed a large amount of barium and fluid retention within the stomach, as well as visualization of the widened jejunal loop. Some barium was also observed in the right half of a nondistended colon. Several calcified lymph nodes were seen to the right of the lower lumbar spine. A roentgenogram of the chest was not done.

Clinically, the patient remained unchanged, and on the third hospital day an operation was performed.

Differential Diagnosis

Dr. S. Peter Sarris*: As the history is recorded in this abstract it appears quite uncomplicated and straightforward. Essentially, it is a history of a sixty-two-year-old man who for four months had symptoms consistent with recurrent high intestinal obstruction. This was further confirmed by the physical examination and the x-ray findings. Furthermore it is fortunate that there was no complicating disease in any of the other systems or any significant past history. In fact the history is so typical of obstructing jejunal neoplasm that one hesitates to make the diagnosis, especially at one of these meetings.

Figure 1.

*Clinical associate in surgery, Massachusetts General Hospital.

Let me go over the history to see if I can emphasize any pertinent evidence of a positive or negative value. The vomitus was very characteristic and very helpful in the diagnosis. It contained undigested food and later food eaten two or three meals before; furthermore, from its color it contained bile, which would place the obstruction distal to the pylorus. The fact that the crampy pains were relieved so easily and promptly by vomiting and that this relief lasted some time would also place the point of the obstruction high in the jejunum. The pains with low intestinal obstruction — lower ileum or large bowel — seldom improve or disappear after vomiting. They may improve slightly, but this relief only lasts a short time. The belching that was mentioned prominently in the history is also helpful in the diagnosis of a high intestinal obstruction. There was a negative gastrointestinal series and a negative Graham test done earlier presumably in another hospital from the statement, "said to be negative." I do not know whether that included a barium-enema examination or just an upper gastrointestinal series and, what is more important, whether it included a motor meal or only a study of the stomach and esophagus. Small-bowel lesions are notoriously missed if the roentgenologist is not instructed specifically to look for them. The pain going up into the back may be significant in indicating involvement of the mesentery of the bowel. The fact that the stools were smaller and lighter is confirmatory evidence of a lesion that was completely obstructing the upper small bowel and preventing food and gastrointestinal juices, particularly bile, from going through.

On physical examination the general appearance was consistent with a slowly progressing obstruction, as was the distention. There was the suggestion of a mass on the left side; I do not know whether that means that there was no mass, just some spasm of the rectus muscle or an elusive mass. Often, before tumor of the small bowel becomes fixed, palpation pushes the tumor among other loops of small bowel, and thus it is made to disappear. The small palpable axillary lymph nodes may be significant. They might be tied up with a lymphoma of the small bowel.

The laboratory data were not significant. There was no leukocytosis, and there was no mention of any stool examination for blood. There are certain questions that I should like to ask the radiologist. Was the mucosa ulcerated or not? Was there evidence of extrinsic or intrinsic narrowing? Was the barium in the right half of the colon found at the same examination as the gastrointestinal series? If it was on the same day, it would suggest a fistula between the small bowel and colon.

Dr. Stanley M. Wyman: As Dr. Sarris has suggested, these films were not all done on the same day. Some films were taken at the time of fluoroscopic examination, and others on the following day. I might say that this is the wrong way to examine this kind of patient. An upper gastrointestinal examination should never be done in any case of small-bowel obstruction. The patient should be intubated and then after he has been cleaned out, a good examination can be made by introducing barium into the tube in the small bowel. This film (Fig. 1) shows fluid levels in the duodenal loop with barium trickling past the ligament of Treitz into the much-distended jejunum. The obstruction lies somewhere in this neighborhood; it cannot be adequately seen on any film. A very small amount of barium is seen to have trickled past this obstruction. These two spot films of the distal loop of jejunum, as far as I can see, fail to demonstrate the mucosa in the narrowed bowel, and I can only assume that there is a narrowed segment there. I cannot make any statement about how the barium got into the right colon in these films taken twenty-four hours later. There is nothing to suggest fistula.

Dr. Sarris: How far into the colon can you see barium?

Dr. Wyman: Up to the left transverse and possibly the descending colon.

Dr. Sarris: Could there be a fistula there?

Dr. Wyman: I do not believe so. The barium has mostly concentrated in the cecum and is strung out from there into the region of the splenic flexure. The point of obstruction may be in the center of this loop.

Dr. Sarris: Can you make a statement whether the narrowed area is a point narrowing, or does it extend a few centimeters?

Dr. Wyman: I cannot even see the narrowing. I can simply assume it is there. That is why I say this is an inadequate examination.

Dr. Sarris: At least it is helpful in making a diagnosis of a high jejunal obstruction.

What lesions in the upper jejunum produce an obstruction like this? Inflammatory reactions, either nonspecific or granulomatous, such as regional enteritis, can occur in the jejunum and can produce isolated lesions, but more commonly they produce multiple lesions. Of course, this could represent the upper lesion of a group of lesions in the small bowel. However, I cannot make that diagnosis. The recurrent bouts of obstruction due to regional enteritis last for days — that is, the inflammation does not subside very suddenly following vomiting. There may be an episode of abdominal pain and vomiting that lasts for a few days and then improvement as the inflammation subsides. Calcified lymph nodes were mentioned, which can indicate tuberculosis, but I think this type of lesion produced by tuberculosis would be extremely rare and there was no evidence of tuberculosis elsewhere. Certainly, calcified lymph nodes like those in the abdomen are very common so that we need not pay too much attention to them.

Adhesions, which can occur without previous operation, are a common cause of intestinal obstruction. This could perfectly well be an attack of jejunal obstruction produced by an adhesion. However, from the history I think I can exclude adhesions. Frequently, in intestinal obstruction from adhesions there is a preceding episode or two of intestinal obstruction but not an acute attack every few days.

Gallstone ileus has become increasingly common. Two things against that, I think, were the negative Graham test and, more important, the fact that gallstone ileus is usually in the lower third of the ileum — not so high in the jejunum. I cannot see any gas in the biliary tree in the x-ray films, and none was reported. Then, too, the four-month history was a little long for gallstone ileus.

Could this stenotic area have been the result of a recurrent volvulus or a recurrent intussusception? Volvulus often recurs. The frequency of attacks and the fact that the obstruction was in the jejunum — the great majority of cases of volvulus are in the ileum and not high in the jejunum — were points against volvulus. In any large series of cases of small-bowel obstruction, there are a few cases in which one finds that there is a stenosis of the small bowel that is not explained pathologically. The stenosis could have resulted from localized mesenteric thrombosis in which the infarction was not sufficient to produce gangrene and perforation but in which there was sufficient ischemia to be followed later by stenosis. The stenotic areas may have been due to an old inflammation, but I cannot make that diagnosis without any preceding episode. I am not going to try to make a diagnosis of stenosis of the small bowel that a pathologist cannot explain.

The most likely condition is a tumor of the small bowel. The commonest tumor obstructing the small bowel is metastatic carcinoma. Even though one excludes cases of metastatic carcinoma in which the primary lesion is obvious, obstruction of the small bowel by metastatic carcinoma is more common than a primary tumor of the small bowel. However, in the absence of any primary lesion I certainly cannot make the diagnosis. At one of the previous conferences when I discussed a small-bowel case, the intestinal obstruction proved to be due to a metastatic carcinoma from the gall bladder. Here there was a negative Graham test. The stomach is a common site. I dare say that in a stomach with so much fluid and so much distention the radiologist might miss a carcinoma. Is that true?

DR. WYMAN: Positively.

DR. SARRIS: Then there might have been a carcinoma of the stomach with a metastatic lesion producing the obstruction in the jejunum. Any other part of the gastrointestinal tract could have been the primary site or even some organ outside the abdomen. In the absence of any hint of a primary lesion somewhere I am going to stick to a primary tumor of the small bowel. What types do we have? The so-called carcinoids constitute roughly a fifth of all the tumors of the small bowel and, as contrasted to the carcinoids of the appendix, often metastasize. However carcinoids are almost always in the ileum. There are very few described in the jejunum. Then there are the sarcomas, including the neurogenic sarcomas, leiomyosarcomas and the lymphosarcomas. I wonder whether the lymph nodes in the axillary area were meant to be significant. There are two points against a sarcoma. Sarcomas increase in incidence as one goes down the gastrointestinal tract. They are more common in the ileum than they are in the jejunum, as against carcinoma, which is more common in the jejunum than in the ileum; sarcomas produce complete obstruction less frequently than carcinomas do. These differences are very small but have to be utilized if I am going to narrow down the diagnosis.

Carcinoma of the small bowel presents itself as a rule in three clinical types: the anemic, the obstructive and the perforative. The patient with the anemic type may have been treated for some time for idiopathic anemia; the obstructive type can produce a clinical picture like this; and the last type can perforate, producing generalized peritonitis, a large abscess or a fistula into another part of the gastrointestinal tract. Of course, many cases dovetail and demonstrate all three features. The case under discussion seemed to fall, if it was such a case, into the obstructive type, with only a slight anemia. Pathologically, the above classification corresponds to three types of lesions, the stenosing type, the polypoid type, with a fair amount of bleeding and a tendency to intussuscept, and the ulcerative type, with massive gastrointestinal bleeding and frequent perforation.

I think I shall make a diagnosis of high jejunal obstruction, and I will guess that this was a primary

carcinoma of the jejunum. My second choice would be a sarcoma, and my third a metastatic lesion. Because of the amount of barium in the colon the possibility of a fistula should also be kept in mind.

DR. PERRY J. CULVER: The x-ray films that were taken outside were done in the office of the patient's physician, who looked for an ulcer. That is what the diagnosis was. Those x-ray films were carried out just through the duodenum. The duodenum was not dilated at that time, two months before admission.

DR. SARRIS: I think that is very important, for early in high small-bowel obstruction, the dilatation of the proximal jejunum is often only transient. If the patient had recently been cleaned out, the upper gastrointestinal tract might perfectly well appear normal in the x-ray film.

DR. GORDON A. DONALDSON: My introduction to this patient was via these x-ray films. With the presence of a mass in the upper abdomen, it was obvious that something would have to be done surgically. However, we did take a few minutes to try to make a preoperative diagnosis. We were disappointed that there were no scars present on the abdomen because we thought this should have been the source of the obstruction — namely, a postoperative adhesion, which is by far the most common cause of obstruction of the small bowel. The calcified lymph node caught our eye, and we thought there might be an adhesion to it, causing the obstruction. This seemed likely in view of the X-Ray Department's definite report that there was no shelf-formation or narrow area in the bowel. Of course, we considered carcinoma, rare as it is, although we were reluctant to make that diagnosis. The Mayo Clinic* has reported a group of 44 cases of primary carcinoma of the jejunum over a forty-year period.

CLINICAL DIAGNOSIS

Jejunal obstruction caused by adhesive band;
? primary carcinoma.

DR. SARRIS'S DIAGNOSIS

Carcinoma of jejunum, with obstruction.
? Sarcoma.
? Metastatic tumor.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of jejunum, with metastases to regional lymph nodes.

PATHOLOGICAL DISCUSSION

DR. DONALDSON: At operation the upper jejunum was greatly distended behind a large nodule in the mesentery of the bowel about 18 inches beyond the ligament of Treitz. The irregular mass was nearly as large as a golf ball. The jejunal mesentery was greatly foreshortened by it, and in the jejunal wall itself was an annular tumor.

DR. BENJAMIN CASTLEMAN: The tumor was a completely annular adenocarcinoma, which had extended through the wall of the bowel to form a mesenteric mass. In addition several of the regional lymph nodes were involved. It was a highly malignant adenocarcinoma.

*Pridgen, J. E., Mayo, C. W., and Dockerty, M. B. Carcinoma of jejunum and ileum exclusive of carcinoid tumors. *Surg., Gynec. & Obst.* 90:513-524, 1950.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. C. Stuart Welch, M.D.
Robert M. Green, M.D. Vernon P. Williams, M.D.
Dwight O'Hara, M.D. Benjamin Castleman, M.D.
Fletcher H. Colby, M.D. Hugh R. Leavell, M.D.
Robert L. Goodale, M.D. J. Englebert Dunphy, M.D.
Chester M. Jones, M.D. Theodore H. Ingalls, M.D.
Harvey R. Morrison, M.D. Deering G. Smith, M.D.*
*Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $9.00 per year (Boston funds); $10.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

STAND-TO

AN OVERWHELMING majority of the people of this country, and indeed of all the democratic countries of the world, have apparently experienced a feeling of relief and a renewal of courage in the knowledge that they are at last facing squarely the realities of their position.

Gratifying as it is, this resoluteness is not unanticipated. It is the expected reaction that comes with the lifting of the load of uncertainty, of indecision, of inactivity and of virtual moral retreat before what almost all recognized as being the greatest danger with which society has yet been threatened.

The battle, on whatever scale it may develop, is now joined; the line is drawn; the point of no return is passed. The latest and most flagrant act of aggression has turned remonstrance into firm resistance. The fact is accepted that this sea of troubles can be ended only by opposing them.

Perhaps this opposition to an unprovoked attack will be successful without a total recourse to arms; but successful it must be, by any means, whatever the nature and despite the magnitude of the assault.

In any event, although especially in the case of a spread of open conflict, the role of the medical profession, great in the last war, will assume still more importance. It is a foregone conclusion that each member of the profession will be found ready to serve in whatever capacity he may be found most useful. It may also be expected that this reserve of highly trained personnel will be employed in the most effective manner.

URGENT BUSINESS

DESPITE the shouting and the tumult, the warnings and the dire forecasts, little has as yet been accomplished in this area for civilian relief in case of widespread need, whether occasioned by military disaster or by some so-called act of God.

A military disaster in the present day, be it said, does not necessarily imply a defeat; it may imply merely an attack. Such an attack is not inevitable, despite the progressive alignment of the nations of the world into two hostile camps, with increasing aggression on the part of one, but if the attack should come, every large city of the country, and particularly those on its seaboards, would immediately be in the front line as much as London was in 1940.

As Bradford indicates elsewhere in this issue of the *Journal*, medical mobilization is of the essence of civilian defense, and medical mobilization until very recent weeks has not merely been neglected in this Commonwealth; it has been omitted altogether. It is quite obvious that casualties in such a total war would be largely civilian, and as Bradford further points out, the enlistment of medical services in the armed forces as previously practiced is entirely wrong. Such a "waste of doctors, improvidently squandered throughout military and naval establishments, idly waiting for action, will be not only inexcusable but insupportable."

The radical step that is recommended is the abolishment of the medical services of Army and Navy and Air Force and combining of their staffs "under a unified medical service whose chief should

be directly subordinate to the Secretary of Defense." Such a department, prepared to treat all sick calls and all casualties, whether civilian or military, "must operate without the blundering interference or control from other services, and without the stupid mismanagement of line officers." Such an organization would resemble that which operated so effectively in Britain during the blitz.

The obvious disadvantage of having the important available hospitals concentrated in the target areas of cities is apparent, and one can but be appalled at the folly of adding to this concentration by building a new Veterans Administration hospital inside the city limits of Boston.

There is at least some encouragement in the knowledge that the Committee on Emergency Medical Service of the Massachusetts Medical Society is actively at work on practical plans for mobilization of physicians, and that a constructive report will shortly be prepared. The Maine Medical Association, independent and foresighted, has had its plan of defense ready for months.

THE DOCTOR'S FEE

As an additional step in the efforts of the Massachusetts Medical Society to develop and maintain good public relations, the Council, at its annual meeting in 1949, appointed a subcommittee of the Committee on Public Relations, "to explore the whole problem of (medical) fees throughout the Commonwealth."

In its report to the Council on May 15, 1950, this committee admitted that there is dissatisfaction on the part of a comparatively few laymen with the charges for professional fees. Little of this dissatisfaction, however, appears to be based on authentic instances of excessive charges that might be considered as above the limits of the patients' ability to pay. Few complaints, furthermore, have come to the attention of the Committee on Public Relations, the Committee on Ethics and Discipline or Massachusetts Medical Service, Inc. Of the specific complaints that have been investigated, the majority seem to result from misunderstandings and are easily adjusted through conferences between physician and patient.

Not only have the physicians in Massachusetts rarely failed to meet the demands of the patient by compromise but they appear to the Committee actually oversensitive to the problem and with a distinct tendency to "lean over backward" in their desire to avoid the criticism of overcharging.

The Committee nevertheless believes that an agreement should be reached by the medical profession of the Commonwealth regarding the principles involved, based on the following factors:

1. The value of the service, whether easily definable, such as fees for a laboratory examination, or relatively indefinite, as fees for anesthesia, roentgenologist's opinion, or such indeterminable value as an unusual operation or a life-saving measure.
2. The nature of the service rendered, with consideration of the technical difficulties, the diagnostic complexity, the length of time consumed and the degree of responsibility assumed.
3. The ability of the patient to pay, with reference to his income, family responsibilities, and the effect upon future income of a long-lasting illness or an ultimately unfavorable prognosis.

The Committee recommends that the fellows of the Massachusetts Medical Society be encouraged to come to an understanding with the patient by free discussion, and that "the attitude of the Society regarding fees and the availability of means for the patient to obtain relief from possible overcharging be publicized by the Committee on Public Relations in whatever manner it may choose to adopt."

This report seems to summarize admirably the complex problem of professional charges, an understanding of which is so vital to the establishment of a satisfactory relationship between the doctor and his patient. The quality of medical care and its cost are the two issues on which good public relations will depend, and the work that the grievance committee may have to do will be largely along these lines.

WIND IN THE WILLOWS

A peripatetic correspondent of the London *Lancet*, in a recent Running Commentary* comments on the "small psychological point . . . which is the basis of a big proportion of road accidents."

The small psychological point that may loom so large upon the road is the sense of power behind

*In England now. *Lancet* 1:923, 1950.

the wheel. It is the zest for aggression with which the world has become so unpleasantly familiar. It is the effect that comes from the possession of a gun, a uniform or political office by one with an unstable personality. It is the epitome of a sense of power that comes to its possessor as it were by accident — from without, and momentarily hiding the true weakness that lies within.

It is the insulation that the inferior person by vicarious means thus seems to acquire against personal contact, and apparently against the necessity of personal responsibility, and against immediate retribution. "Insulation, power and a platform" the circumambulatory correspondent of the *Lancet* finds "in a car or in becoming a national leader."

Those who are familiar with *The Wind in the Willows* will find in Mr. Toad of Toad Hall, the bully of the highway of 1910, the exact counterpart of a million motorists of 1950, and the motivating force behind many another type of aggressor.

The whole of Dr. Ware's article on Croup, inserted in the 12th and 13th Nos. of this volume of the Journal, is copied into the Ohio Medical and Surgical Journal, without any credit being given, or a word of intimation as to the source whence it was obtained.

Boston M. & S. J., *July 31, 1850*

BOOK REVIEW

Essential Urology. By Fletcher H. Colby, M.D. 12°, cloth, 580 pp., with 342 illustrations. Baltimore: Williams and Wilkins Company, 1950. $8.00.

The first paragraph of the author's preface accurately describes the purpose for which this compact and useful volume was written:

> To give the important facts of the embryology, anatomy, physiology and diseases of the genitourinary organs. It does not pretend to be a comprehensive textbook of urology.
>
> To many it may seem brief and incomplete, but I wish the book to be brief; neither an outline, nor an unwieldy volume containing unessential details.

The author has accomplished his purpose extraordinarily well. He emphasizes the sound principles for the study and diagnosis of patients with genitourinary disease, and he pays particular attention to the necessary and important bearing of embryology, anatomy and physiology on these diseases. The reviewer was particularly impressed by the clear anatomic drawings showing the lymphatic drainage of the genitourinary-tract organs — a subject too often somewhat neglected in teaching. The sections on pathology, gross and microscopical, are comprehensive and yet concise, and here, again, the illustrations are useful and adequate. As the author states in his preface, little emphasis has been placed on treatment because he intended this volume mainly to be for students and because treatment is ever-changing in these modern days. He emphasizes the broader basic principles of treatment rather than falling into the too common mistake of overdetailed descriptions of therapy.

One has no hesitation in enthusiastically recommending this volume for what it is intended to be — namely, "essential urology." It should prove very useful to students in this field and, in particular, for those who are training themselves for greater proficiency as urologists.

CORRESPONDENCE

THE CALL FOR VOLUNTEERS

To the Editor: On June 25, on the thirty-eighth parallel in Korea, a blow was struck at the freedom of the world, more nakedly aggressive than those directed at Poland in 1939 and at the United States at Pearl Harbor in 1941.

No American can escape the challenge. Doctor, lawyer, merchant, chief — all are involved, directly or indirectly. It is the doctor with whom this communication is concerned.

The American Medical Association has already taken steps to urge doctors who received deferment from Selective Service during World War II, as well as financial aid from the Government, to complete their medical education, to volunteer *now* for field duty. This appeal should be expedited to its goal by all ethical means of communication.

The Army needs young medical officers for duty with combat troops — not next year or next month, but *now*. The recent graduates of ASTP, especially those who have had no service with the armed forces, have a strong moral obligation to be among the first to support other young men who are defending their country, which is and for an indefinite period must be the bulwark of the United Nations. Hospitals and teaching institutions must be willing to relinquish interns and residents of this category — not next year or next month, but *now*.

This is not all. The President has the power to order the National Guard and organized reserves to extended active federal service. No one can foresee how much farther, even, than the limits suggested in the President's speech of July 19, the mobilization of the armed forces must go. The present strength of the Medical Corps reserve is not adequate to cover even the complete mobilization envisaged by Senator Lodge. Every active medical reservist known to me at the present time is prepared for the call whenever it may come. They may not suffice. Medical veterans of World War II are no longer as young as they were five years ago: there is need for new men of good will to fill the ranks, *now*. The great teaching hospitals and medical schools should prepare to implement the affiliation program of the Army, *now*. It is later than we think.

THOMAS R. GOETHALS, M.D.

Boston, Massachusetts

NOTICES

VOLUNTEERS FOR ACTIVE DUTY IN NAVY MEDICAL, DENTAL AND NURSE CORPS

Owing to the shortage of physicians, dentists and nurses to meet present obligations, the Surgeon General of the Navy asks that these members of the inactive naval reserve volunteer immediately for extended active duty. Medical and dental officers in the ranks of commander and below and nurses in the ranks of lieutenant and below will be accepted.

The recently authorized increase in the over-all manpower strength of the Navy requires the services of additional Medical Department personnel to serve in the continental United States and overseas.

Qualified civilian physicians, dentists and nurses may apply for active duty in the Medical, Dental and Nurse Corps of the United States Naval Reserve. Physicians and dentists will be commissioned in ranks up to and including lieutenant commander, and nurses in ranks up to and including lieutenant, depending upon age and professional experience.

Interns in civilian hospitals are urged to apply for a commission in the rank of lieutenant (junior grade) in the Navy Medical Corps Reserve and have the remainder of their intern training sponsored by the Navy.

For additional information regarding commission and appointment, application should be made to the nearest Office of Naval Officer Procurement.

(*Notices concluded on page xvii*)